```
=> file registry
FILE 'REGISTRY' ENTERED AT 14:38:41 ON 19 JUL 2006
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STRUCTURE FILE UPDATES:   18 JUL 2006  HIGHEST RN 894196-03-3
DICTIONARY FILE UPDATES:  18 JUL 2006  HIGHEST RN 894196-03-3

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
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REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 14:38:45 ON 19 JUL 2006
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AUTHOR SEARCH

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FILE COVERS 1907 - 19 Jul 2006  VOL 145 ISS 4
FILE LAST UPDATED: 18 Jul 2006  (20060718/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d stat que L33
L31          12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DEWDNEY N?/AU
L32        1091 SEA FILE=HCAPLUS ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L33           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 AND L32


=> d stat que L34
L3               STR
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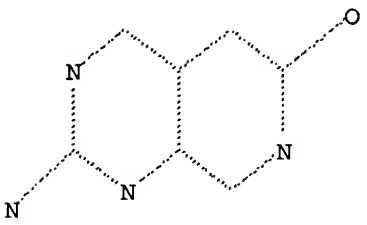

Structure attributes must be viewed using STN Express query preparation.

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L5             7 SEA FILE=REGISTRY SSS FUL L3
L6             2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5
L31           12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DEWDNEY N?/AU
L32         1091 SEA FILE=HCAPLUS ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L34            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L31 OR L32) AND L6


=> d stat que L35
L31           12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DEWDNEY N?/AU
L32         1091 SEA FILE=HCAPLUS ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L35           23 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L31 OR L32) AND (P38/OBI OR
                 P 38/OBI)


=> s L33-L35
L45           23 (L33 OR L34 OR L35)

=> file marpat
FILE 'MARPAT' ENTERED AT 14:39:29 ON 19 JUL 2006
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FILE CONTENT: 1961-PRESENT VOL 145 ISS 1 (20060714/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US   2006118302 08 JUN 2006
DE 102004053653 04 MAY 2006
EP      1653548 03 MAY 2006
JP   2006112980 27 APR 2006
WO   2006053912 26 MAY 2006
GB      2419594 03 MAY 2006
FR      2877004 28 APR 2006
RU      2275374 27 APR 2006
CA      2518664 10 MAR 2006

Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.


=> d stat que L39
L3              STR
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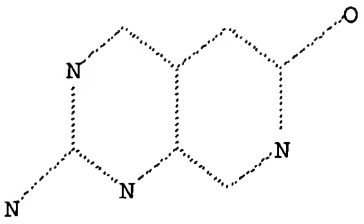

Structure attributes must be viewed using STN Express query preparation.
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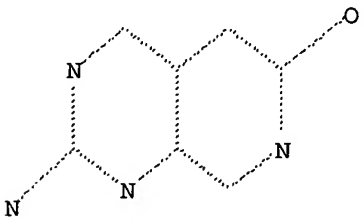
L19 STR



Structure attributes must be viewed using STN Express query preparation.
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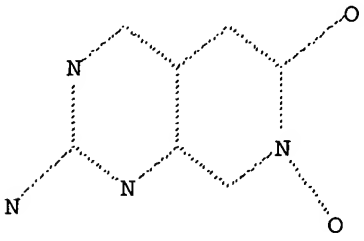
L22 STR



Structure attributes must be viewed using STN Express query preparation.
L24 2 SEA FILE=MARPAT SUB=L15 SSS FUL L22
L31 12 SEA FILE=HCAPLUS ABB=ON PLU=ON DEWDNEY N?/AU
L32 1091 SEA FILE=HCAPLUS ABB=ON PLU=ON GOLDSTEIN D?/AU
L37 4 SEA FILE=MARPAT ABB=ON PLU=ON L31
L38 20 SEA FILE=MARPAT ABB=ON PLU=ON L32
L39 1 SEA FILE=MARPAT ABB=ON PLU=ON (L37 OR L38) AND (L21 OR L24)

=> file wpix
FILE 'WPIX' ENTERED AT 14:40:18 ON 19 JUL 2006
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FILE LAST UPDATED: 14 JUL 2006 <20060714/UP>
MOST RECENT DERWENT UPDATE: 200645 <200645/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,

```
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BIX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> d stat que L42
L40             4 SEA FILE=WPIX ABB=ON  PLU=ON  DEWDNEY N?/AU
L41            97 SEA FILE=WPIX ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L42             3 SEA FILE=WPIX ABB=ON  PLU=ON  L40 AND L41


=> d stat que L43
L28             1 SEA FILE=WPIX ABB=ON  PLU=ON  (RAFUWH/DCN OR RAFUWI/DCN OR
                  RAFUWJ/DCN OR RAFUWK/DCN OR RAFUWL/DCN)
L29             1 SEA FILE=WPIX ABB=ON  PLU=ON  (979788-1-0-0/DCRE OR 979789-0-0-
                  0/DCRE OR 979790-0-0-0/DCRE OR 979791-0-0-0/DCRE OR 979792-0-0-
                  0/DCRE)
L30             1 SEA FILE=WPIX ABB=ON  PLU=ON  L28 OR L29
L40             4 SEA FILE=WPIX ABB=ON  PLU=ON  DEWDNEY N?/AU
L41            97 SEA FILE=WPIX ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L43             1 SEA FILE=WPIX ABB=ON  PLU=ON  (L40 OR L41) AND L30


=> s L42-L43
L46             3 (L42 OR L43)

=> => dup rem L45 L46 L39
FILE 'HCAPLUS' ENTERED AT 14:41:05 ON 19 JUL 2006
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FILE 'WPIX' ENTERED AT 14:41:05 ON 19 JUL 2006
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FILE 'MARPAT' ENTERED AT 14:41:05 ON 19 JUL 2006
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PROCESSING COMPLETED FOR L45
PROCESSING COMPLETED FOR L46
PROCESSING COMPLETED FOR L39
L47            24 DUP REM L45 L46 L39 (3 DUPLICATES REMOVED)
                  ANSWERS '1-23' FROM FILE HCAPLUS
                  ANSWER '24' FROM FILE WPIX

=> d ibib abs hitind hitstr L47 1-23; d ibib abs hitstr L47 24

L47  ANSWER 1 OF 24  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER:        2005:983769  HCAPLUS
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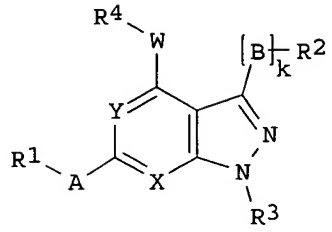
DOCUMENT NUMBER: 143:286445
TITLE: Preparation of fused pyrazolo pyrimidine and pyrazolo pyrimidinone derivatives as **p38** kinase inhibitors
INVENTOR(S): Arora, Nidhi; Billedeau, Roland Joseph; **Dewdney, Nolan James**; Gabriel, Tobias; **Goldstein, David Michael**; O'Yang, Counde; Soth, Michael
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 90 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005197340	A1	20050908	US 2005-67336	20050225
WO 2005085249	A1	20050915	WO 2005-EP1936	20050224

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-548583P P 20040227
OTHER SOURCE(S): MARPAT 143:286445
GI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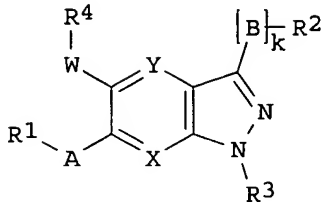
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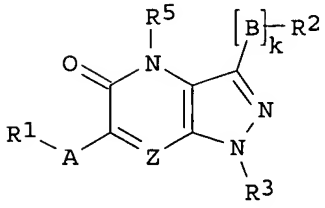
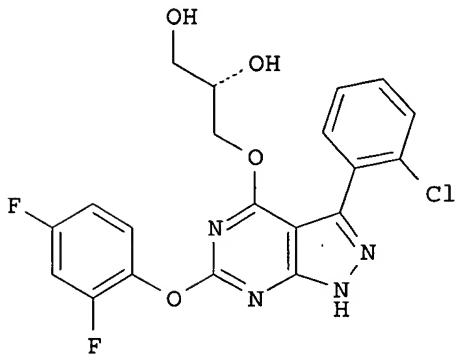

III


IV

AB The title compds. I-III [R1 = (hetero)aryl, aralkyl, cycloalkyl; R2 = (hetero)aryl, cycloalkyl, alkyl, heterocyclyl; R3 = H, alkyl; R4 = H, alkyl, OH, etc.; R5 = H, alkyl, heteroalkyl, etc.; X, Y = N, or one of X and Y = N and the other = CR6 (R6 = H, alkyl, OH, etc.); Z = N, CR6; W = O, SOm, CH2, (un)substituted NH; m = 0-2; A = O, CH2, SOm, C(O), etc.; B = O, SOm, C(O), etc.; k = 0-1], useful in treating p38 mediated disorders, were prepared and formulated. E.g., a multi-step synthesis of (S)-IV, starting from 4,6-dichloro-2-(methylthio)pyrimidine and 2-chlorobenzaldehyde, was given. The compds. I were found to be inhibitors of p38 MAP kinase. IV showed a p38 IC50 of 0.004 μM.

IC ICM A61K031-519
ICS A61K031-498; C07D487-02
INCL 514249000; 514262100; 544256000; 544330000
CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
ST fused pyrazolo pyrimidine pyrimidinone prepn **p38** kinase inhibitor; pyrazolopyrimidine prepn **p38** kinase inhibitor; pyrazolopyrimidinone prepn **p38** kinase inhibitor
IT Inflammation
(Crohn's disease, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)
IT Intestine, disease
(Crohn's, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)
IT Respiratory distress syndrome
(adult, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)
IT Lung, disease
(chronic obstructive pulmonary disease, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)
IT Intestine, disease
(irritable bowel syndrome, treating; preparation of pyrazolopyrimidine and

pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT Antiarthritics
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT Arthritis
(treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT 165245-96-5, **p38** Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT 864299-82-1P 864300-75-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT 864298-62-4P 864298-63-5P 864298-64-6P 864298-66-8P 864298-68-0P
864298-69-1P 864298-71-5P 864298-73-7P 864298-75-9P 864298-77-1P
864298-79-3P 864298-80-6P 864298-81-7P 864298-82-8P 864298-83-9P
864298-84-0P 864298-85-1P 864298-86-2P 864298-87-3P 864298-88-4P
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864300-76-5P 864300-77-6P 864300-78-7P 864300-79-8P 864300-80-1P
864300-81-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT 89-98-5, 2-Chlorobenzaldehyde 98-98-6, 2-Pyridinecarboxylic acid 367-27-1, 2,4-Difluorophenol 872-53-7, Cyclopentanecarboxaldehyde 918-05-8, N,N-Dimethyl methanesulfonamide 1979-98-2, 2-(Methylsulfanyl)pyrimidine-4,6-diol 2799-17-9, (S)-1-Amino-2-propanol 3512-17-2, 2,4,6-Trifluoropyridine 3900-89-8, 2-Chlorophenylboronic acid 4774-14-5, 2,6-Dichloropyrazine 5334-40-7 6299-25-8, 4,6-Dichloro-2-(methylthio)pyrimidine 14347-78-5 76513-69-4, (2-Chloromethoxyethyl)trimethylsilane 449811-63-6 864301-27-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT 33097-11-9P 55864-87-4P 85426-79-5P 864300-82-3P 864300-83-4P 864300-84-5P 864300-85-6P 864300-86-7P 864300-87-8P 864300-88-9P 864300-89-0P 864300-90-3P 864300-91-4P 864300-92-5P 864300-93-6P 864300-94-7P 864300-95-8P 864300-96-9P 864300-97-0P 864300-98-1P 864300-99-2P 864301-00-8P 864301-01-9P 864301-02-0P 864301-03-1P 864301-04-2P 864301-05-3P 864301-06-4P 864301-07-5P 864301-08-6P 864301-09-7P 864301-10-0P 864301-11-1P 864301-12-2P 864301-13-3P 864301-14-4P 864301-15-5P 864301-16-6P 864301-17-7P 864301-18-8P 864301-19-9P 864301-20-2P 864301-21-3P 864301-22-4P 864301-23-5P 864301-24-6P 864301-25-7P 864301-26-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

this one

L47 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:878160 HCAPLUS
DOCUMENT NUMBER: 141:366244
TITLE: Preparation of substituted 7-azaquinazoline compounds as **p38** kinase inhibitors
INVENTOR(S): **Dewdney, Nolan James; Goldstein, David Michael**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004209903	A1	20041021	US 2004-824980	20040415
AU 2004229163	A1	20041028	AU 2004-229163	20040413
CA 2520785	AA	20041028	CA 2004-2520785	20040413
WO 2004091625	A1	20041028	WO 2004-EP3883	20040413

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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1620105	A1	20060201	EP 2004-726958		20040413
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BR 2004009405	A	20060425	BR 2004-9405		20040413
CN 1774250	A	20060517	CN 2004-80009956		20040413
PRIORITY APPLN. INFO.:			US 2003-463229P	P	20030416
			WO 2004-EP3883	W	20040413

OTHER SOURCE(S): MARPAT 141:366244

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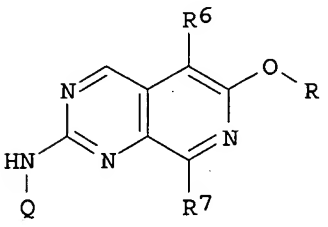

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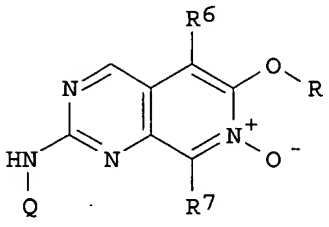

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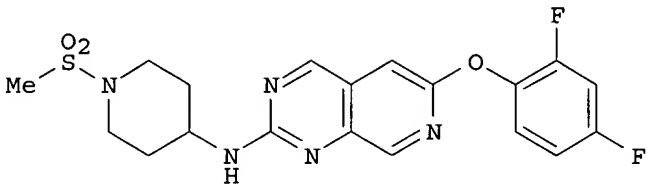


III

AB The title compds. [I or II; R = (un)substituted alkyl, cycloalkyl, aryl; R6 = H, alkyl; R7 = H, a non-interfering substituent such as alkyl, halo, etc.; Q = a non-aromatic moiety such as alkyl, cycloalkyl, heterocyclyl] which are useful as p38 kinase inhibitors, were prepared and formulated. E.g., a multi-step synthesis of III, starting from 2-chloro-4-methyl-5-nitropyridine, which showed IC50 of <0.05μM against p38 MAP kinase, was given.

IC ICM A61K031-519
ICS C07D487-02

INCL 514264110; 544280000

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST azaquinazoline prepn formulation **p38** MAP kinase inhibitor

IT Inflammation
(Crohn's disease, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Intestine, disease
(Crohn's, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Respiratory distress syndrome
(adult, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Lung, disease
(chronic obstructive pulmonary disease, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Heart, disease

(infarction, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Antiasthmatics
Human
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Inflammation
Spinal column, disease
(spondylitis, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Brain, disease
(stroke, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Alzheimer's disease
Arthritis
Asthma
Sepsis
(treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT 165245-96-5, **p38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

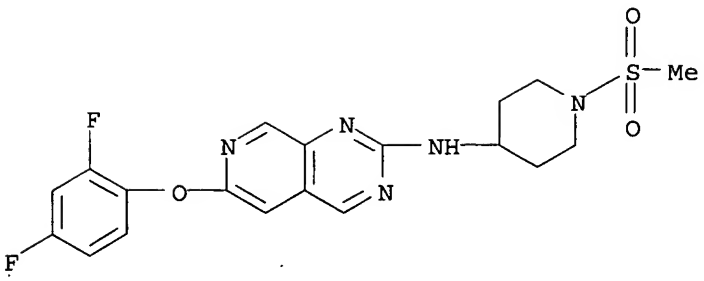
IT **777899-52-2P 777899-53-3P 777899-54-4P**
777899-55-5P 777899-56-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT 367-27-1, 2,4-Difluorophenol 23056-33-9, 2-Chloro-4-methyl-5-nitropyridine 402927-97-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

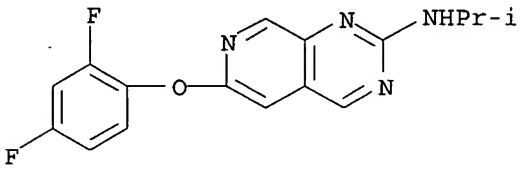
IT 777899-57-7P 777899-58-8P 777899-59-9P 777899-60-2P 777899-61-3P
777899-62-4P 777899-63-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT **777899-52-2P 777899-53-3P 777899-54-4P**
777899-55-5P 777899-56-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

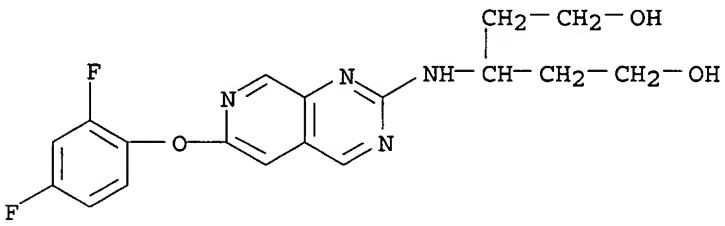
RN 777899-52-2 HCAPLUS
CN 4-Piperidinamine, N-[6-(2,4-difluorophenoxy)pyrido[3,4-d]pyrimidin-2-yl]-1-(methylsulfonyl)- (9CI) (CA INDEX NAME)



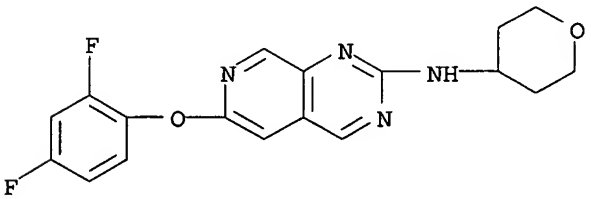
RN 777899-53-3 HCAPLUS
CN Pyrido[3,4-d]pyrimidin-2-amine, 6-(2,4-difluorophenoxy)-N-(1-methylethyl)-(9CI) (CA INDEX NAME)



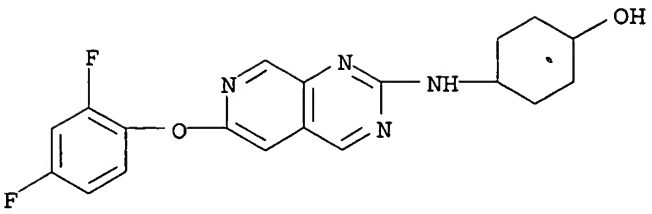
RN 777899-54-4 HCAPLUS
CN 1,5-Pentanediol, 3-[[6-(2,4-difluorophenoxy)pyrido[3,4-d]pyrimidin-2-yl]amino]- (9CI) (CA INDEX NAME)



RN 777899-55-5 HCAPLUS
CN Pyrido[3,4-d]pyrimidin-2-amine, 6-(2,4-difluorophenoxy)-N-(tetrahydro-2H-pyran-4-yl)- (9CI) (CA INDEX NAME)



RN 777899-56-6 HCAPLUS
CN Cyclohexanol, 4-[[6-(2,4-difluorophenoxy)pyrido[3,4-d]pyrimidin-2-yl]amino]- (9CI) (CA INDEX NAME)



L47 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:123964 HCAPLUS
DOCUMENT NUMBER: 144:369962
TITLE: Discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an Orally Bioavailable and Highly Selective Inhibitor of **p38** Map Kinase
AUTHOR(S): **Goldstein, David M.**; Alfredson, Tom; Bertrand, Jay; Browner, Michelle F.; Clifford, Ken; Dalrymple, Stacie A.; Dunn, James; Freire-Moar, Jose; Harris, Seth; Labadie, Sharada S.; La Fargue, JoAnn; Lapierre, Jean Marc; Larrabee, Susan; Li, Fujun; Papp, Eva; McWeeney, Daniel; Ramesha, Chakk; Roberts, Rick; Rotstein, David; San Pablo, Bong; Sjogren, Eric B.; So, On-Yee; Talamas, Francisco X.; Tao, Will; Trejo, Alejandra; Villasenor, Armando; Welch, Mary; Welch, Teresa; Weller, Paul; Whiteley, Phyllis E.; Young, Kelly; Zipfel, Sheila
CORPORATE SOURCE: Roche Palo Alto LLC, Palo Alto, CA, 94304, USA
SOURCE: Journal of Medicinal Chemistry (2006), 49(5), 1562-1575
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel class of highly selective inhibitors of p38 MAP kinase was discovered from high throughput screening. The synthesis and optimization of a series of 5-amino-N-phenyl-1H-pyrazol-4-yl-3-phenylmethanones is described. An X-ray crystal structure of this series bound in the ATP binding pocket of unphosphorylated p38α established the presence of a unique hydrogen bond between the exocyclic amine of the inhibitor and threonine 106 which likely contributes to the selectivity for p38. The crystallog. information was used to optimize the potency and physicochem. properties of the series. The incorporation of the 2,3-dihydroxypropoxy moiety on the pyrazole scaffold resulted in a compound with excellent drug-like properties including high oral bioavailability. These efforts identified RO3201195 as an orally bioavailable and highly selective inhibitor of p38 which was selected for advancement into Phase I clin. trials.

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT Human
(discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)

IT 165245-96-5, **p38** Map kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable

and highly selective inhibitor of **p38** Map kinase)

IT 249936-55-8P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)

IT 249936-11-6P 249936-69-4P 882175-25-9P 882175-29-3P 882175-38-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)

IT 33064-14-1P 54606-37-0P 249935-58-8P 249935-59-9P 249935-60-2P
249935-61-3P 249935-62-4P 249935-64-6P 249935-74-8P 249935-82-8P
249936-01-4P 249936-10-5P 249936-33-2P 249936-38-7P 249936-41-2P
249936-47-8P 249936-48-9P 249936-54-7P 882175-13-5P 882175-14-6P
882175-15-7P 882175-16-8P 882175-17-9P 882175-18-0P 882175-19-1P
882175-20-4P 882175-21-5P 882175-22-6P 882175-24-8P 882175-26-0P
882175-27-1P 882175-28-2P 882175-32-8P 882175-33-9P 882175-34-0P
882175-36-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)

IT 75-05-8, Acetonitrile, reactions 89-25-8, 3-Methyl-1-phenyl-5-pyrazolone
93-58-3, Methyl benzoate 94-05-3, Ethyl (ethoxymethylene)cyanoacetate
98-88-4, Benzoyl chloride 100-63-0, Phenylhydrazine 107-19-7,
Propargyl alcohol 109-01-3, 1-Methylpiperazine 110-89-4, Piperidine,
reactions 371-14-2, 4-Fluorophenylhydrazine 529-27-1,
2-Methylphenylhydrazine 540-51-2, 2-Bromoethanol 586-75-4,
4-Bromobenzoyl chloride 614-16-4, Benzoylacetonitrile 618-89-3, Methyl
3-bromobenzoate 619-27-2, 3-Nitrophenylhydrazine 619-44-3, Methyl
4-iodobenzoate 622-15-1, N,N'-Diphenylformamidine 658-27-5,
3-Fluorophenylhydrazine 1692-15-5, 4-Pyridinylboronic acid 1878-67-7,
3-Bromophenylacetic acid 2127-03-9, 2,2'-Dipyridinyl disulfide
2368-80-1, 2-Fluorophenylhydrazine 2386-58-5, Vinylsulfonamide
3471-32-7, 4-Methoxyphenylhydrazine 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 5368-81-0, Methyl 3-methoxybenzoate
18312-46-4, 2-Methoxyphenylhydrazine 19438-10-9, Methyl
3-hydroxybenzoate 23735-43-5 23788-74-1 58313-23-8, Ethyl
3-iodobenzoate 79629-41-7, 2-Bromoallyloxymethylbenzene 131534-65-1
197958-29-5, 2-Pyridinylboronic acid 249937-07-3 747413-17-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)

IT 6123-64-4P 28229-69-8P, 2-(3-Bromophenyl)ethanol 70591-86-5P,
3-Bromobenzoylacetonitrile 138907-68-3P 187949-90-2P 247206-80-0P
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249937-10-8P 249937-11-9P 249937-12-0P 249937-13-1P 249937-22-2P
249937-23-3P 249937-25-5P 249937-44-8P 249937-47-1P 331777-15-2P
882175-23-7P 882175-30-6P 882175-31-7P 882175-35-1P 882175-37-3P
882175-39-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-

dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1004746 HCAPLUS
DOCUMENT NUMBER: 143:306308
TITLE: Preparation of heteroaryl-fused pyrazolo derivatives as inhibitors of **p38** kinase
INVENTOR(S): Arora, Nidhi; Billedeau, Roland J.; **Dewdney, Nolan James**; Gabriel, Tobias; **Goldstein, David Michael**; Soth, Michael; Trejo-Martin, Teresa Alejandra
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.; McCaleb, Kristin Lynn
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005085248	A1	20050915	WO 2005-EP1815	20050222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005203091	A1	20050915	US 2005-65890	20050225
PRIORITY APPLN. INFO.:			US 2004-548642P P	20040227

OTHER SOURCE(S): MARPAT 143:306308
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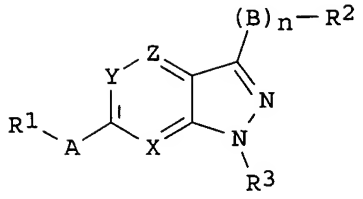

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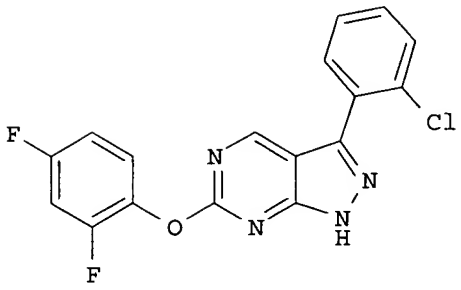

II

AB Title compds. I [R1 = (un)substituted aryl, heteroaryl or cycloalkyl; R2 = (un)substituted aryl, heteroaryl, alkyl, etc.; R3 = H or alkyl; one or two of X, Y and Z is N, and the other is CR4; R4 independently = H, alkyl, halo, etc.; A = O, CO, CH2, etc.; n = 0-1; B = O, CO, CH=CH, etc.] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of p38 kinase. Thus, e.g., II was prepared by cyclization of (2-chlorophenyl)-(4-chloro-2-methylsulfanylpyrimidin-5-yl)-methanone (preparation given) with hydrazine followed by oxidation to the resp. sulfonyl derivative and subsequent coupling with 2,4-difluorophenol. The inhibitory activity of I against p38 kinase was determined by measuring the transfer of the γ-phosphate from γ-33P-ATP by p38 kinase to Myelin Basic Protein (MBP) and it was revealed that compds. of the invention were inhibitors of p38 kinase, with one compound displaying an IC50 value of approx. 0.01 μM. I as inhibitors of p38 kinase should prove useful in the treatment of arthritis, Crohn's disease or chronic obstructive pulmonary disease. Pharmaceutical compns. comprising I are disclosed.

IC ICM C07D487-04
ICS C07D471-04; A61K031-4162; A61K031-4985; A61K031-519; A61P019-02; A61P025-28; C07D239-00; C07D231-00; C07D241-00

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST heteroaryl fused pyrazolo deriv prepn inhibitor **p38** kinase antiarthritic

IT Inflammation
(Crohn's disease; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)

IT Intestine, disease
(Crohn's; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)

IT Respiratory distress syndrome
(adult; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)

IT Lung, disease
(chronic obstructive pulmonary disease; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)
IT Intestine, disease
(irritable bowel syndrome; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)
IT Anti-inflammatory agents
(nonsteroidal; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)
IT Alzheimer's disease
Anti-Alzheimer's agents
Antiarthritics
Arthritis
Inflammation
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)
IT 165245-96-5, **p38** Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)
IT 864301-19-9P 864301-20-2P 864542-52-9P 864542-54-1P 864542-56-3P
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864543-45-3P 864543-46-4P 864543-47-5P 864543-48-6P 864543-49-7P
864543-51-1P 864543-52-2P 864543-53-3P 864543-55-5P 864543-56-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)
IT 89-98-5, 2-Chlorobenzaldehyde 108-12-3, Isovaleryl chloride 122-51-0, Triethyl orthoformate 348-54-9, 2-Fluoroaniline 367-25-9, 2,4-Difluoroaniline 367-27-1, 2,4-Difluorophenol 532-27-4, 2-Chloroacetophenone 1996-44-7, 2,4-Difluorothiophenol 2402-78-0, 2,6-Dichloropyridine 3900-89-8, 2-Chlorophenylboronic acid 4774-14-5, 2,6-Dichloropyrazine 16750-63-3, 2-Methoxyphenylmagnesium bromide 18368-64-4, 2-Chloro-5-methylpyridine 36082-50-5, 5-Bromo-2,4-dichloropyrimidine 49844-90-8, 4-Chloro-2-(methylthio)pyrimidine 298709-29-2 679406-03-2, 4,6-Dichloropyridazine-3-carboxylic acid ethyl ester
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)
IT 20173-49-3P 60323-96-8P 60868-43-1P 205985-98-4P 864301-16-6P
864301-17-7P 864301-18-8P 864543-57-7P 864543-58-8P 864543-60-2P

864543-61-3P 864543-62-4P 864543-63-5P 864543-64-6P 864543-65-7P
864543-66-8P 864543-67-9P 864543-68-0P 864543-69-1P 864543-70-4P
864543-71-5P 864543-72-6P 864543-73-7P 864543-74-8P 864543-75-9P
864543-76-0P 864543-77-1P 864543-78-2P 864543-79-3P 864543-80-6P
864543-81-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of **p38** kinase)

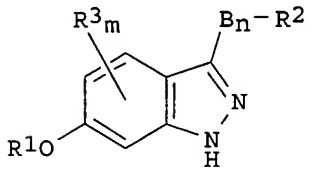
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

No

L47 ANSWER 5 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1004715 HCAPLUS
DOCUMENT NUMBER: 143:306306
TITLE: Preparation of indazole derivatives as **p38** MAP kinase inhibitors
INVENTOR(S): Arora, Nidhi; Gabriel, Tobias; **Goldstein, David Michael**; Trejo-Martin, Teresa Alejandra
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005085206	A1	20050915	WO 2005-EP1816	20050222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005215595	A1	20050929	US 2005-65979	20050225

PRIORITY APPLN. INFO.: US 2004-548585P P 20040227
OTHER SOURCE(S): MARPAT 143:306306
GI



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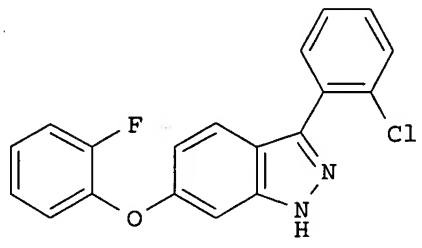


II

AB Title compds. represented by the formula I [wherein R1, R2 = independently

(hetero)aryl, aralkyl, cycloalkyl; m = 0-4; R3 = H, (halo)alkyl, cyano, amino, etc.; n = 0 or 1; B = O, SOj, CH(OR), (alkyl)amino or CO; j = 0-2; R = H or alkyl; and pharmaceutically acceptable salts, solvates or prodrugs thereof] were prepared as p38 MAP (Mitogen-activated protein) kinase inhibitors. For example, II was given in a multi-step synthesis starting from the reaction of 4-fluoro-2-nitrotoluene with 2-fluorophenol. 4-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenol exhibited a p38 IC50 (μM) of 0.028. Thus, I and their pharmaceutical compns. are useful for the treatment of p38 mediated disorders, such as arthritis, Crohns disease and irritable bowel syndrome, in a patient (no data).

IC ICM C07D231-56
ICS A61K031-416; A61P025-28; A61P029-00

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST phenoxy aryl indazole prepn **p38** MAP kinase inhibitor; arthritis Crohn Alzheimer inflammation Lung disease treatment phenoxyindazole prepn

IT Inflammation
(Crohn's disease; preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT Intestine, disease
(Crohn's; preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT Respiratory distress syndrome
(adult; preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT Lung, disease
(chronic obstructive pulmonary disease; preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT Intestine, disease
(irritable bowel syndrome; preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT Alzheimer's disease
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarthritics
Arthritis
Human
Inflammation
(preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT 165245-96-5, **p38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT 864500-29-8P, 6-(2-Fluorophenoxy)-3-phenyl-1H-indazole 864500-30-1P, 3-(2-Chlorophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-31-2P, 6-(2-Fluorophenoxy)-3-(3-methoxyphenyl)-1H-indazole 864500-32-3P, 6-(2-Fluorophenoxy)-3-(4-methoxyphenyl)-1H-indazole 864500-33-4P, 3-(5-Bromo-2-methoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-34-5P, 6-(2-Fluorophenoxy)-3-(thiophen-3-yl)-1H-indazole 864500-35-6P, 6-(2-Fluorophenoxy)-3-(o-tolyl)-1H-indazole 864500-36-7P, 6-(2-Fluorophenoxy)-3-(4-methoxy-2-methylphenyl)-1H-indazole 864500-37-8P, 3-(Benzo[b]thiophen-3-yl)-6-(2-fluorophenoxy)-1H-indazole 864500-38-9P, 6-(2-Fluorophenoxy)-3-(2-methoxyphenyl)-1H-indazole 864500-39-0P, 3-(2,5-Dimethoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-40-3P, 3-(2-Chlorophenyl)-5-(2-fluorophenoxy)-1H-indazole 864500-41-4P 864500-42-5P, 6-(2-Fluorophenoxy)-3-(furan-3-yl)-1H-indazole 864500-43-6P, 3-(3-Benzyloxyphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-44-7P, 3-(3-Chloro-4-propoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-45-8P, 6-(2-Fluorophenoxy)-3-(3-isopropoxyphenyl)-1H-

indazole 864500-46-9P, 3-(3,5-Dimethylphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-47-0P, [4-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenyl]dimethylamine 864500-48-1P, 6-(2-Fluorophenoxy)-3-(4-isopropoxyphenyl)-1H-indazole 864500-49-2P, 3-(Benzo[b]thiophen-2-yl)-6-(2-fluorophenoxy)-1H-indazole 864500-50-5P, 6-(2-Fluorophenoxy)-3-(2-trifluoromethylphenyl)-1H-indazole 864500-51-6P, 6-(2-Fluorophenoxy)-3-(m-tolyl)-1H-indazole 864500-52-7P, 6-(2-Fluorophenoxy)-3-(p-tolyl)-1H-indazole 864500-53-8P, 3-(4-Chlorophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-54-9P, 3-(Biphenyl-4-yl)-6-(2-fluorophenoxy)-1H-indazole 864500-55-0P, 6-(2-Fluorophenoxy)-3-(1H-indol-3-yl)-1H-indazole 864500-56-1P, 3-(3-Chlorophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-57-2P, 3-(3,4-Dimethoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-58-3P, 3-(4-Bromophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-59-4P, 6-(2-Fluorophenoxy)-3-(3,4,5-trimethoxyphenyl)-1H-indazole 864500-60-7P, 6-(2-Fluorophenoxy)-3-[4-(pyridin-3-yl)phenyl]-1H-indazole 864500-61-8P, N-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenylamine 864500-62-9P, 4-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenol
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

IT 367-12-4, 2-Fluorophenol 446-10-6, 4-Fluoro-2-nitrotoluene 3900-89-8, 2-Chlorophenylboronic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

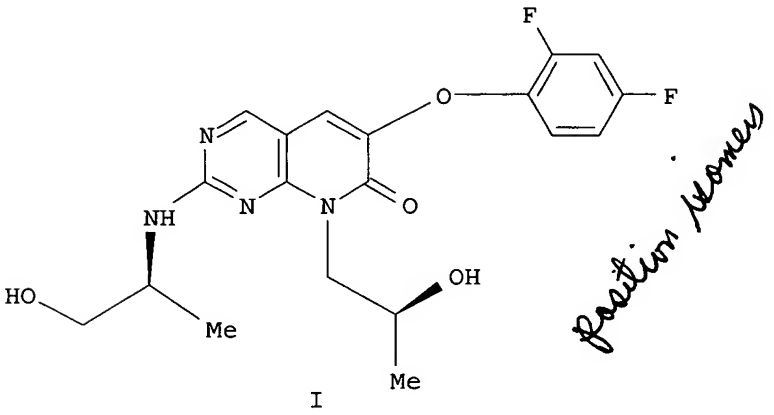
IT 864500-63-0P, 4-(2-Fluorophenoxy)-2-nitrotoluene 864500-64-1P, [5-(2-Fluorophenoxy)-2-methylphenyl]amine 864500-65-2P, 6-(2-Fluorophenoxy)-1H-indazole 864500-66-3P, 6-(2-Fluorophenoxy)-3-iodo-1H-indazole 864500-67-4P, 6-(2-Fluorophenoxy)-3-iodoindazole-1-carboxylic acid tert-butyl ester 864500-68-5P, 3-(2-Chlorophenyl)-6-(2-fluorophenoxy)indazole-1-carboxylic acid tert-butyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 6-phenoxy-indazole derivs. as **p38** MAP kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:431405 HCAPLUS
DOCUMENT NUMBER: 142:482053
TITLE: Preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders
INVENTOR(S): **Goldstein, David Michael**
PATENT ASSIGNEE(S): Roche Palo Alto Llc, USA
SOURCE: U.S. Pat. Appl. Publ., 36 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005107408	A1	20050519	US 2004-987656	20041112
AU 2004289428	A1	20050526	AU 2004-289428	20041104
CA 2544247	AA	20050526	CA 2004-2544247	20041104

WO 2005047284 A1 20050526 WO 2004-EP12475 20041104
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2003-519789P P 20031113
WO 2004-EP12475 W 20041104
OTHER SOURCE(S): MARPAT 142:482053
GI



I

positional isomers

AB Compds. such as I were prepared for treating p38 mediated disorders in a patient. I was prepared starting from Et 4-chloro-2-methylthiopyrimidine-5-carboxylate and (S)-1-amino-2-propanol and involving a number of intermediates. I and other compds. were evaluated using a p38 mitogen-activated protein kinase in vitro assay.

IC ICM A61K031-519
ICS C07D487-02
INCL 514264110; 544279000
CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
ST hydroxyalkyl pyridopyrimidinone deriv prepn **p38** kinase mediated disorder
IT Inflammation
(Crohn's disease; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)
IT Intestine, disease
(Crohn's; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)
IT Respiratory distress syndrome
(adult; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)
IT Intestine, disease

(irritable bowel syndrome; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT Lung, disease
(obstructive; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT Alzheimer's disease
Antiarthritics
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT 165245-96-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT 449808-64-4 449809-71-6 449809-86-3 449809-99-8 449810-69-9
449811-01-2 449811-92-1 851885-74-0 851885-75-1 851885-76-2
851885-77-3 851885-78-4 851885-79-5 851885-80-8 851885-81-9
851885-82-0 851885-83-1 851885-84-2 851885-85-3 851885-86-4
851885-87-5 851885-88-6
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT 851885-55-7P 851885-56-8P 851885-57-9P 851885-58-0P 851885-59-1P
851885-60-4P 851885-61-5P 851885-62-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT 124-68-5 717-30-6 2749-11-3, (S)-2-Amino-1-propanol 2799-17-9, (S)-1-Amino-2-propanol 5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT 2799-16-8P 35320-23-1P 851885-63-7P 851885-64-8P 851885-65-9P
851885-66-0P 851885-67-1P 851885-68-2P 851885-69-3P 851885-70-6P
851885-71-7P 851885-72-8P 851885-73-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

IT 851885-89-7 851885-90-0 851885-91-1 851885-92-2 851885-93-3
851885-94-4 851885-95-5 851885-96-6 851885-97-7 851885-98-8
851885-99-9 851886-00-5 851886-01-6 851886-02-7 851886-03-8
851886-04-9 851886-05-0 851886-06-1 851886-07-2 851886-08-3
851886-09-4 851886-10-7 851886-11-8 851886-12-9 851886-13-0
851886-14-1 851886-15-2 851886-16-3 851886-17-4 851886-18-5
851886-19-6 851886-20-9 851886-21-0 851886-22-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating **p38** kinase mediated disorders)

L47 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1131486 HCAPLUS
DOCUMENT NUMBER: 143:431843
TITLE: Pathway to the clinic: Inhibition of **P38** MAP kinase. A review of ten chemotypes selected for development
AUTHOR(S): **Goldstein, David M.**; Gabriel, Tobias

CORPORATE SOURCE: Department of Medicinal Chemistry, Roche Palo Alto, Palo Alto, CA, 94304, USA
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2005), 5(10), 1017-1029
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. P38 mitogen activated protein (MAP) kinase remains the most compelling therapeutic target for oral drug intervention for a wide range of autoimmune disorders based on the central role this enzyme plays in inflammatory cell signaling. Efforts to discover inhibitors of p38 suitable for clin. investigation have continued to escalate in part due to the incredible diversity of unique chemotypes reported to inhibit the enzyme. Since 1993, at least seventeen p38 inhibitors have been reported to have entered into clin. trials. Next generation inhibitors have been disclosed with improved potency for p38 and enhanced selectivity vs. other protein kinases. Over the last three years, there have been multiple reports of cytokine suppression in humans following oral administration of p38 inhibitors. These results, in addition to proof of concept studies in rheumatoid patients, have established p38 inhibition as an avenue for the future management of pro-inflammatory cytokine based diseases. This review describes the discovery at Roche of novel p38 inhibitors which have advanced into clin. trials. The pharmacol. of the Roche compds. is then compared with eight chemical distinct p38 inhibitors known to have entered clin. development.

CC 1-0 (Pharmacology)

IT Autoimmune disease
Drug design
Drug discovery
Drug targets
Human
(development **P38** MAP kinase inhibitors)

IT Drug delivery systems
(oral; development **P38** MAP kinase inhibitors)

IT Structure-activity relationship
(**p38** MAPK inhibiting; development **P38** MAP kinase inhibitors)

IT 165245-96-5, **P38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; development **P38** MAP kinase inhibitors)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 8 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:143149 HCAPLUS
DOCUMENT NUMBER: 140:199338
TITLE: Preparation of 6-alkoxy-pyridopyrimidines as **p**-**38** MAP kinase inhibitors
INVENTOR(S): **Goldstein, David Michael**; Lim, Julie Anne
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

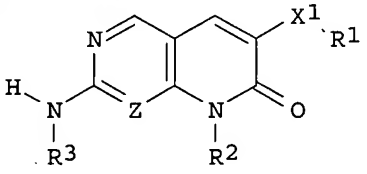
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004014907		A1	20040219	WO 2003-EP8357		20030729
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW					
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2492112		AA	20040219	CA 2003-2492112		20030729
AU 2003251661		A1	20040225	AU 2003-251661		20030729
EP 1539755		A1	20050615	EP 2003-784102		20030729
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003013297		A	20050621	BR 2003-13297		20030729
CN 1675207		A	20050928	CN 2003-818688		20030729
JP 2006507236		T2	20060302	JP 2004-526812		20030729
US 2004038999		A1	20040226	US 2003-634936		20030805
US 6965030		B2	20051115			
US 2005203300		A1	20050915	US 2005-121862		20050504
PRIORITY APPLN. INFO.:				US 2002-401491P	P	20020806
				WO 2003-EP8357	W	20030729
				US 2003-634936	A3	20030805

OTHER SOURCE(S): MARPAT 140:199338

GI

position isomer see cited ref



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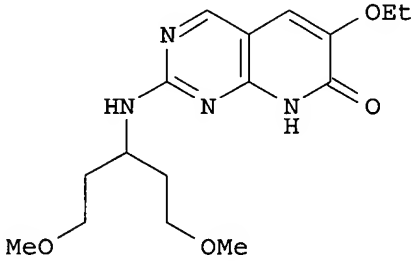


II

AB The title compds. [I; R1 = alkyl, cycloalkyl, cycloakylalkyl, or CH2(alkenyl); X1 = O, NH, N(alkyl), S, CO; Z = N, CH; R2 = H, alkyl, cycloalkyl, etc.; R3 = alkyl, haloalkyl, aryl, etc.], were prepared E.g., a 3-step synthesis of II (starting from 4-amino-2-butylsulfanyl-4,5-dihydropyrimidine-5-carboxaldehyde and Et ethoxyacetate) which showed IC50 of about 7.7 μM in p38 MAP kinase in vitro assay, was given. The pharmaceutical composition comprising the compound I is claimed.

IC ICM C07D471-04
ICS A61K031-519; A61P029-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST alkoxypyridopyrimidine prepn **p38** MAP kinase inhibitor; pyridopyrimidine alkoxy prepn **p38** MAP kinase inhibitor

IT Inflammation
(Crohn's disease, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)

IT Intestine, disease
(Crohn's, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)

IT Respiratory distress syndrome
(adult, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT Inflammation
Spinal column, disease
(ankylosing spondylitis, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT Lung, disease
(chronic obstructive pulmonary disease, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT Intestine, disease
(inflammatory, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT Intestine, disease
(irritable bowel syndrome, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT Anti-Alzheimer's agents
Anti-inflammatory agents
Antiasthmatics
Antirheumatic agents
Human
(preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT Arthritis
(psoriatic arthritis, treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT Alzheimer's disease
Asthma
Psoriasis
Rheumatoid arthritis
(treatment of; preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT 165245-96-5, **p38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT 661450-66-4P 661450-67-5P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT 661450-62-0P 661450-63-1P 661450-64-2P 661450-65-3P 661450-68-6P
661450-69-7P 661450-70-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT 817-95-8, Ethyl ethoxyacetate 2032-34-0, 3,3-Diethoxypropanenitrile
5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate
6290-49-9, Methyl methoxyacetate 28177-48-2, 2,6-Difluorophenol
38041-19-9, 4-Aminotetrahydropyran 58859-46-4, Ethyl
4-amino-1-piperidinecarboxylate 661450-77-7 661450-78-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)
IT 770-31-0P, 4-Amino-2-(methylthio)pyrimidine-5-carboxaldehyde
17759-30-7P, 4-Methylamino-2-methylthiopyrimidine-5-methanol

76360-82-2P, Ethyl 4-(methylamino)-2-(methylthio)pyrimidine-5-carboxylate 102669-01-2P 105161-35-1P 185040-32-8P, 4-Methylamino-2-methylthiopyrimidine-5-carboxaldehyde 185040-33-9P 185040-34-0P 185040-35-1P, 4-Ethylamino-2-methylthiopyrimidine-5-carboxaldehyde 449808-49-5P 449810-42-8P 449811-11-4P 661450-71-1P 661450-72-2P 661450-73-3P 661450-74-4P 661450-75-5P 661450-76-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 6-alkoxy-pyridopyrimidines as **p-38** MAP kinase inhibitors)

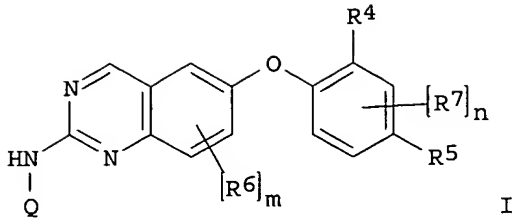
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 9 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:878161 HCAPLUS
DOCUMENT NUMBER: 141:366245
TITLE: Preparation of substituted quinazolines as **p38** kinase inhibitors
INVENTOR(S): Dunn, James Patrick; **Goldstein, David Michael**; Stahl, Christoph Martin; Trejo-Martin, Teresa Alejandra
PATENT ASSIGNEE(S): F. Hoffmann-La Roche AG, USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004209904	A1	20041021	US 2004-824731	20040415
AU 2004230209	A1	20041028	AU 2004-230209	20040408
CA 2522522	AA	20041028	CA 2004-2522522	20040408
WO 2004092144	A2	20041028	WO 2004-EP3779	20040408
WO 2004092144	A3	20050324		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1620408	A2	20060201	EP 2004-726448	20040408
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
BR 2004009580	A	20060418	BR 2004-9580	20040408
CN 1774425	A	20060517	CN 2004-80010341	20040408

PRIORITY APPLN. INFO.: US 2003-463467P P 20030416
WO 2004-EP3779 W 20040408

OTHER SOURCE(S): MARPAT 141:366245
GI



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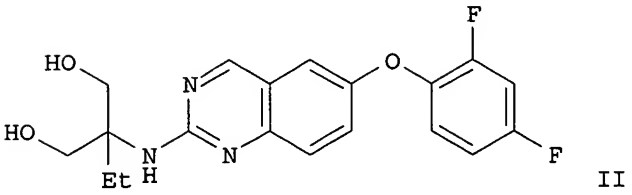

II

AB The title compds. I [R4, R5 = H, halo, CN, haloalkyl, or haloalkoxy (but are not both hydrogen); R6, R7 = alkyl, halo, CN, etc.; Q = a non-aromatic moiety; m = 0-3; n = 0-2] which are useful as p38 kinase inhibitors, were prepared and formulated. E.g., a multi-step synthesis of II, starting from Me 5-chloro-2-nitrobenzoate and 2,4-difluorophenol, which showed IC50 of <0.10 μM against p38 MAP kinase, was given.

IC ICM A61K031-517
ICS C07D043-02

INCL 514266200; X51-426.64; X54-428.4; X54-429.3

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST quinazoline prepn formulation **p38** MAP kinase inhibitor

IT Inflammation
(Crohn's disease, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Intestine, disease
(Crohn's, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Respiratory distress syndrome
(adult, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Lung, disease
(chronic obstructive pulmonary disease, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Heart, disease
(infarction, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Antiasthmatics
Human
(preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Inflammation
Spinal column, disease
(spondylitis, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Brain, disease
(stroke, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT Alzheimer's disease

Arthritis
Asthma
Sepsis
(treating; preparation of substituted quinazolines as **p38** kinase inhibitors)

IT 165245-96-5, **p38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of substituted quinazolines as **p38** kinase inhibitors)

IT 778639-17-1P 778639-18-2P 778639-19-3P 778639-20-6P 778639-21-7P
778639-22-8P 778639-23-9P 778639-24-0P 778639-25-1P 778639-26-2P
778639-27-3P 778639-28-4P 778639-29-5P 778639-30-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted quinazolines as **p38** kinase inhibitors)

IT 115-70-8, 2-Amino-2-ethyl-1,3-propanediol 367-27-1, 2,4-Difluorophenol 18542-42-2, 2-(Methylsulfanyl)ethylamine 51282-49-6, Methyl 5-chloro-2-nitrobenzoate 402927-97-3, 1-(Methylsulfonyl)piperidin-4-amine 778639-39-7, 2-Chloro-6-ethoxyquinazoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted quinazolines as **p38** kinase inhibitors)

IT 778639-31-9P 778639-32-0P 778639-33-1P 778639-34-2P 778639-35-3P
778639-36-4P 778639-37-5P 778639-38-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted quinazolines as **p38** kinase inhibitors)

L47 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:796707 HCAPLUS
DOCUMENT NUMBER: 139:307789
TITLE: Preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase
INVENTOR(S): **Goldstein, David Michael**; Hawley, Ronald Charles; Lui, Alfred Sui-ting; Sjogren, Eric Brian
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003082871	A1	20031009	WO 2003-EP3178	20030327
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2479644	AA	20031009	CA 2003-2479644	20030327
AU 2003215675	A1	20031013	AU 2003-215675	20030327
BR 2003008937	A	20050104	BR 2003-8937	20030327
EP 1492790	A1	20050105	EP 2003-745276	20030327
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK						
CN 1646529	A	20050727	CN 2003-807536			20030327
JP 2006503802	T2	20060202	JP 2003-580336			20030327
US 2003232847	A1	20031218	US 2003-406364			20030403
US 6949560	B2	20050927				
US 2005197352	A1	20050908	US 2005-122137			20050504
PRIORITY APPLN. INFO.:			US 2002-369929P		P	20020403
			WO 2003-EP3178		W	20030327
			US 2003-406364		A3	20030403

OTHER SOURCE(S): MARPAT 139:307789

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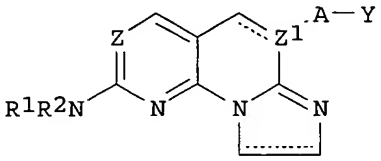

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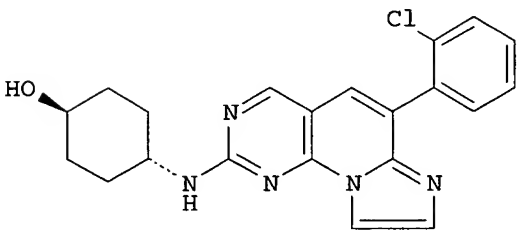

II

AB Title compds. I [Z = N, CH; Z1 = N, CH, C; R1 = H, alkyl; R2 = (un)substituted alkyl, aralkyl, cycloalkyl, heterocyclyl, aryl; A = bond, O, S, s(O), SO2, (un)substituted CH2, NH, CO; Y = alkyl, heterocyclic, (un)substituted cycloalkyl, aryl, heteroaryl] were prepared for use as inhibitors of p-38 kinase. Thus, the title compound II was prepared by treating 4-amino-2-benzylthiopyrimidine-5-carboxaldehyde with 2-ClC6H4CH2CN, cyclizing with ClCH2CHClOEt, oxidizing to the sulfoxide, and reaction with trans-4-aminocyclohexanol. II had IC50 for inhibition of p-38 kinase of 0.01 μM.

IC ICM C07D471-14
ICS C07D487-14; A61K031-519; A61P025-00; A61P029-00; A61P011-00; C07D239-00; C07D235-00; C07D221-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST imidazopyridopyrimidine prepn **p38** kinase inhibitor

IT Inflammation
(Crohn's disease; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Intestine, disease
(Crohn's; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Respiratory distress syndrome
(adult; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Lung, disease
(chronic obstructive pulmonary disease; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Intestine, disease
(irritable bowel syndrome; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)
IT Alzheimer's disease
Antiarthritics
Arthritis
Human
(preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)
IT 165245-96-5, **p-38** Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)
IT 610785-97-2P 610785-99-4P 610786-02-2P 610786-03-3P 610786-08-8P 610786-09-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)
IT 124-68-5, 2-Amino-2-methyl-1-propanol 140-75-0, 4-Fluorobenzylamine 371-40-4, 4-Fluoroaniline 623-46-1, 1,2-Dichloro-1-ethoxyethane 1072-72-6, Tetrahydrothiopyran-4-one 2856-63-5, 2-Chlorophenylacetonitrile 3891-07-4, N-(2-Hydroxyethyl)phthalimide 24115-20-6, 4-Fluorophenoxyacetonitrile 27489-62-9, trans-4-Aminocyclohexanol 38041-19-9, Tetrahydropyran-4-amine 49773-20-8, 2-Methylsulfonylethylamine 50541-93-0, 4-Amino-1-benzylpiperidine 335318-13-3 335318-29-1 402740-45-8 610786-18-0 610786-19-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)
IT 6309-59-7P, Tetrahydrothiopyran-4-one oxime 21926-00-1P, 4-Aminotetrahydrothiopyran 182223-53-6P 182223-54-7P 210240-20-3P 402927-96-2P 402927-97-3P 402927-98-4P 402927-99-5P 449809-32-9P 610786-10-2P 610786-11-3P 610786-12-4P 610786-13-5P 610786-15-7P 610786-16-8P 610786-17-9P 610786-20-4P 610786-22-6P 610786-23-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)
IT 610785-98-3P 610786-00-0P 610786-01-1P 610786-04-4P 610786-05-5P 610786-06-6P 610786-07-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:719487 HCAPLUS
DOCUMENT NUMBER: 139:246044
TITLE: Bicyclic pyridine and pyrimidine derivatives, e.g., thieno[2,3-d]pyrimidines and analogs, active as **p38** kinase inhibitors, and their preparation, pharmaceutical compositions, and uses
INVENTOR(S): Chen, Jian Jeffrey; **Dewdney, Nolan James**; Stahl, Christoph Martin
PATENT ASSIGNEE(S): F. Hoffman-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 80 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003074530	A1	20030912	WO 2003-EP2090		20030228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2477721	AA	20030912	CA 2003-2477721		20030228
AU 2003210388	A1	20030916	AU 2003-210388		20030228
EP 1485390	A1	20041215	EP 2003-743361		20030228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003008232	A	20041228	BR 2003-8232		20030228
CN 1639168	A	20050713	CN 2003-805419		20030228
JP 2005526057	T2	20050902	JP 2003-572998		20030228
US 2003207900	A1	20031106	US 2003-383392		20030306
US 2005288312	A1	20051229	US 2005-202611		20050812
US 2006084803	A1	20060420	US 2005-292217		20051130
PRIORITY APPLN. INFO.:			US 2002-362373P	P	20020307
			US 2002-430508P	P	20021203
			WO 2003-EP2090	W	20030228
			US 2003-383392	A1	20030306

OTHER SOURCE(S): MARPAT 139:246044
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention discloses compds. I, their pharmaceutical formulations, methods of making them, and their uses in the treatment of p38 kinase-mediated diseases [wherein: A is N or CH; R1 is H, alkyl or arylalkyl; R2 is alkyl, hydroxyalkyl, (R'')2NCO-alkylene- (where each R'' is independently H or alkyl), cycloalkyl, heterocyclyl, aryl, heteroaryl, or heteroalkyl; X is O, NR3, or S, wherein R3 is H, alkyl, or aryl; and Y is bond, O, NR', CO, CH(OR'), CH(R'), or S(O)n, wherein n = 0-2; and R' is H or alkyl; and R is aryl or heteroaryl; or an isomer, a pharmaceutically acceptable salt, an ester, or a prodrug thereof]. The compds. are useful for treatment of disorders exacerbated or caused by excessive or unregulated TNF or p38 kinase production Claimed methods of treatment include uses for treatment of arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease. A table of over 40 compds. I is given, and most of these compds. are also claimed individually. The example compds. are mostly thienopyrimidines, but include some furanopyrimidines and pyrrolopyrimidines. For instance, invention compound II (as the HCl salt) was prepared from 4-chloro-2-(methylthio)pyrimidine in 5 steps: (1)

fluorination of chloro using KF and 18-crown-6 in tetraglyme; (2) lithiation in the 5-position with LDA and formylation with EtOCHO; (3) cyclocondensation of the resultant aldehyde with 2'-ClC6H4COCH2SH to form a fused thiophene ring; (4) oxidation of the methylthio group to a Me sulfone using Oxone; and (5) aminolysis of the sulfone with 4-aminotetrahydropyran, followed by chromatog. and acidification in ether. In a test for inhibition of recombinant p38 kinase in vitro, invention compound III gave an IC50 of 104 nM.

IC ICM C07D495-04
ICS C07D487-04; C07D491-04; A61K031-519; A61P019-02

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST bicyclic pyridine pyrimidine prepn **p38** kinase inhibitor TNF; thienopyrimidine furanopyrimidine pyrrolopyrimidine prepn treatment arthritis Crohn Alzheimer ARDS

IT Inflammation
(Crohn's disease, treatment of; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT Intestine, disease
(Crohn's, treatment of; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT Respiratory distress syndrome
(adult, treatment of; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT Lung, disease
(chronic obstructive pulmonary disease, treatment of; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of biosynthesis; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT Intestine, disease
(irritable bowel syndrome, treatment of; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Human
(preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT Alzheimer's disease
Arthritis
(treatment of; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 598298-05-6P, 2-(Methylsulfinyl)-6-benzylfurano[2,3-d]pyrimidine
RL: BYP (Byproduct); PREP (Preparation)
(byproduct; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 598297-63-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 598297-55-3P 598297-56-4P 598297-57-5P 598297-58-6P 598297-59-7P, 2-[(Tetrahydropyran-4-yl)amino]-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine
598297-60-0P 598297-61-1P 598297-62-2P 598297-64-4P 598297-65-5P
598297-66-6P 598297-67-7P 598297-68-8P 598297-69-9P 598297-70-2P
598297-71-3P 598297-72-4P 598297-73-5P 598297-74-6P 598297-75-7P
598297-76-8P 598297-77-9P 598297-78-0P 598297-79-1P 598297-80-4P
598297-81-5P 598297-82-6P, 2-[(Tetrahydropyran-4-yl)amino]-6-

benzylfurano[2,3-d]pyrimidine 598297-83-7P, 2-(Cyclopentylamino)-6-benzylfurano[2,3-d]pyrimidine 598297-84-8P, 2-[(4-Hydroxycyclohexyl)amino]-6-benzylfurano[2,3-d]pyrimidine 598297-85-9P, 2-[(Tetrahydropyran-4-yl)amino]-6-(2-methoxybenzoyl)-7-methylpyrrolo[2,3-d]pyrimidine 598297-86-0P, 2-(Cyclopentylamino)-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598297-87-1P, 2-[(4-Hydroxycyclohexyl)amino]-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598297-88-2P, 2-[(Tetrahydropyran-4-yl)amino]-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598297-89-3P 598297-90-6P 598297-91-7P, 2-(Isopropylamino)-6-benzylfurano[2,3-d]pyrimidine 598297-92-8P, 2-(Phenylamino)-6-(4-methoxyphenyl)-7-phenylpyrrolo[2,3-d]pyrimidine 598297-93-9P, 2-[[1-(2-Hydroxyethyl)-3-hydroxypropyl]amino]-6-(2-methoxybenzoyl)thieno[2,3-d]pyrimidine 598297-94-0P, [6-[(2,4-Difluorophenyl)sulfanyl]thieno[2,3-d]pyrimidin-2-yl](tetrahydropyran-4-yl)amine 598297-95-1P, [6-(2,4-Difluorophenoxy)thieno[2,3-d]pyrimidin-2-yl](tetrahydropyran-4-yl)amine 598297-96-2P, [6-(Phenylsulfanyl)thieno[2,3-d]pyrimidin-2-yl](tetrahydropyran-4-yl)amine 598297-97-3P, 2-[(1,1-Dioxotetrahydro-2H-thiopyran-4-yl)amino]-6-(3-fluorobenzoyl)thieno[2,3-d]pyrimidine 598297-98-4P, 2-[(Tetrahydropyran-4-yl)amino]-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine hydrochloride 598297-99-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 165245-96-5, **p-38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 5000-66-8P, 2-Bromo-2'-chloroacetophenone 14080-51-4P 17759-30-7P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-methanol 76360-82-2P, Ethyl 4-(methylamino)-2-(methylthio)pyrimidine-5-carboxylate 117516-97-9P 161124-03-4P, 4-Fluoro-2-(methylthio)pyrimidine 161124-07-8P, 4-Fluoro-2-(methylthio)pyrimidine-5-carboxaldehyde 175657-37-1P, 2-(Acetylthio)-2'-chloroacetophenone 185040-32-8P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-carboxaldehyde 309976-36-1P 595565-59-6P, 2'-Chloro-2-thioacetophenone 598298-00-1P 598298-01-2P, 2-(Methanesulfonyl)-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine 598298-02-3P, 2-(Methylthio)-6-(2-methoxybenzoyl)-7-methylpyrrolo[2,3-d]pyrimidine 598298-03-4P 598298-04-5P, 2-(Methylsulfonyl)-6-benzylfurano[2,3-d]pyrimidine 598298-06-7P, 2-(Methylthio)-5-(3-phenylpropyn-1-yl)-6-(methylamino)pyrimidine 598298-07-8P, 2-(Methylthio)-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598298-08-9P, 2-(Methanesulfinyl)-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598298-09-0P, (Tetrahydropyran-4-yl)(thieno[2,3-d]pyrimidin-2-yl)amine 598298-10-3P 598298-11-4P, 4-Chloro-2-(methanesulfonyl)thieno[2,3-d]pyrimidine 598298-12-5P, 2-(Methanesulfonyl)thieno[2,3-d]pyrimidine 598298-13-6P, (6-Iodothieno[2,3-d]pyrimidin-2-yl)(tetrahydropyran-4-yl)amine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 107-91-5, Cyanoacetamide 367-27-1, 2,4-Difluorophenol 882-33-7, Phenyl disulfide 1003-03-8, Aminocyclopentane 1996-44-7, 2,4-Difluorobenzenethiol 2142-68-9, 2'-Chloroacetophenone 5909-24-0, Ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate 10147-11-2, 3-Phenyl-1-propyne 31949-21-0, 2'-Methoxy-2-bromoacetophenone 38041-19-9, 4-Aminotetrahydropyran 40018-26-6, 2,5-Dihydroxy-1,4-

dithiane 49844-90-8, 4-Chloro-2-(methylthio)pyrimidine 76510-61-7, 2-(Methylthio)-4-hydroxy-5-iodopyrimidine 111079-19-7, 2-(Methanethio)-4-chloro-5-iodopyrimidine
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:202633 HCAPLUS
DOCUMENT NUMBER: 138:238019
TITLE: Preparation of 5-(3-pyridyl)pyrrol-2-amines as antiinflammatory agents
INVENTOR(S): **Goldstein, David Michael**; Rotstein, David Mark
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003020715	A1	20030313	WO 2002-EP9505		20020826
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2458808	AA	20030313	CA 2002-2458808		20020826
EP 1423378	A1	20040602	EP 2002-767427		20020826
EP 1423378	B1	20051109			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002012077	A	20040928	BR 2002-12077		20020826
CN 1547578	A	20041117	CN 2002-816631		20020826
JP 2005506324	T2	20050303	JP 2003-524985		20020826
AT 309239	E	20051115	AT 2002-767427		20020826
ES 2252509	T3	20060516	ES 2002-2767427		20020826
US 2003130319	A1	20030710	US 2002-231792		20020829
US 6696471	B2	20040224			
PRIORITY APPLN. INFO.:			US 2001-316169P	P	20010830
			WO 2002-EP9505	W	20020826

OTHER SOURCE(S): MARPAT 138:238019
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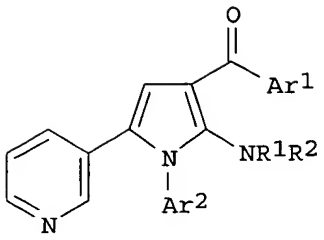


I

AB The title compds. [I; Ar1, Ar2 = (un)substituted aryl; R1, R2 = H, alkyl, N-protecting group] and their pharmaceutically acceptable salts, useful in the treatment of inflammatory diseases, especially arthritis, were prepared and formulated. Thus, alkylation of benzoylacetonitrile with 3-bromoacetylpyridine.HBr in the presence of NaH in THF followed by reacting 2-benzoyl-4-oxo-4-(pyridin-3-yl)butyronitrile with 4-fluoroaniline in the presence of concentrate HCl afforded I [Ar1 = Ph; Ar2 = 4-FC6H4; R1, R2 = H] which showed IC50 of 1.64x10-1 μM against p-38 MAP kinase.

IC ICM C07D401-04
ICS A61K031-4025; A61P029-00

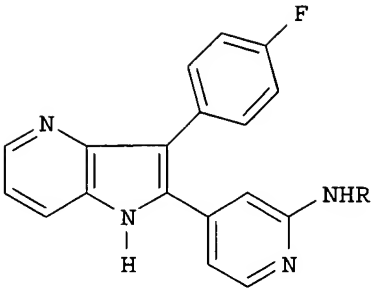
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

ST pyridylpyrroleamine prepn formulation antiinflammatory antiarthritic **p38** MAP kinase; pyrrolamine pyridyl prepn formulation **p38** MAP kinase inhibitor

IT 165245-96-5, **p38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 5-(3-pyridyl)pyrrol-2-amines as antiinflammatory agents)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:738803 HCAPLUS
DOCUMENT NUMBER: 139:307697
TITLE: Design and Synthesis of 4-Azaindoles as Inhibitors of **p38** MAP Kinase
AUTHOR(S): Trejo, Alejandra; Arzeno, Humberto; Browner, Michelle; Chanda, Sushmita; Cheng, Soan; Comer, Daniel D.; Dalrymple, Stacie A.; Dunten, Pete; Lafargue, JoAnn; Lovejoy, Brett; Freire-Moar, Jose; Lim, Julie; McIntosh, Joel; Miller, Jennifer; Papp, Eva; Reuter, Deborah; Roberts, Rick; Sanpablo, Florentino; Saunders, John; Song, Kyung; Villasenor, Armando; Warren, Stephen D.; Welch, Mary; Weller, Paul; Whiteley, Phyllis E.; Zeng, Lu; **Goldstein, David M.**
CORPORATE SOURCE: Department of Medicinal Chemistry, Roche Palo Alto LLC, Palo Alto, CA, 94304, USA
SOURCE: Journal of Medicinal Chemistry (2003), 46(22), 4702-4713
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:307697
GI



I

AB Inhibition of the biosynthesis of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 via p38 has been an approach toward the development of a disease modifying agent for the treatment of chronic inflammation and autoimmune diseases. The development of a new core structure of p38 inhibitors, 3-(4-fluorophenyl)-2-(pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine, is described. X-ray crystallog. data of the lead bound to the active site of p38 was used to guide the optimization of the series. Specific focus was placed on modulating the phys. properties of the core while maintaining potent inhibition of p38. These efforts identified I [R = (R)-2-hydroxypropyl] as a potent inhibitor of p38, which also possessed the required phys. properties worthy of advanced studies.

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27, 75

ST crystal structure **p38** MAP kinase; azaindole prepn inhibitor **p38** MAP kinase

IT Crystal structure
Molecular structure
(of **p38** MAP kinase)

IT Human
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 165245-96-5, **p38** MAP Kinase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(crystal structure; preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 34810-03-2, **p38**, biological studies 610270-98-9 610270-99-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 610270-90-1P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 223743-49-5
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 223738-94-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 223738-90-7P 223738-97-4P 223739-06-8P 223739-61-5P 223739-79-5P
223739-97-7P 223740-56-5P 223740-67-8P 223742-68-5P 610270-66-1P
610270-76-3P 610270-93-4P 610270-94-5P 610270-95-6P 610270-96-7P
610270-97-8P 610271-00-6P 610271-01-7P 610271-02-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 62-53-3, Aniline, reactions 79-08-3 106-40-1, 4-Bromoaniline
106-49-0, 4-Methylaniline, reactions 109-77-3, Malononitrile 371-40-4,
4-Fluoroaniline 459-22-3, 4-Fluorophenylacetonitrile 540-51-2
872-85-5, 4-Formylpyridine 874-24-8 1120-87-2, 4-Bromopyridine
1194-02-1, 4-Fluorobenzonitrile 2459-09-8 2799-16-8,
(R)-2-Hydroxypropylamine 2799-17-9, (S)-2-Hydroxypropylamine
4595-59-9, 5-Bromopyrimidine 5349-17-7 5470-18-8, 2-Chloro-3-nitropyridine 6168-72-5, 2-Hydroxy-1-methylethylamine 6298-19-7,
3-Amino-2-chloropyridine 6482-24-2 13325-10-5, 4-Hydroxybutylamine
13552-21-1, 2-Hydroxybutylamine 14254-57-0, Isonicotinoyl chloride
42802-94-8 54035-94-8 56477-57-7 70298-89-4 116332-54-8
130387-74-5, 4-Fluorophenylmagnesium chloride 610271-05-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 73406-50-5P, Ethyl 3-hydroxypicolinate 115858-97-4P 115858-98-5P
153254-91-2P 223738-89-4P 223742-77-6P 223742-81-2P 223742-86-7P
223742-89-0P 223742-93-6P 223742-96-9P 223743-15-5P 223743-18-8P
223743-21-3P 223743-23-5P 223743-26-8P 223743-28-0P 223743-30-4P
610270-69-4P 610270-72-9P 610270-74-1P 610270-84-3P 610270-86-5P
610270-88-7P 610270-92-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 610271-03-9P 610271-04-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

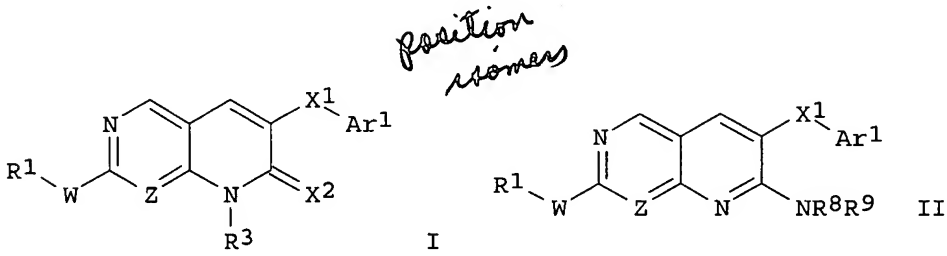
L47 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:637680 HCAPLUS
DOCUMENT NUMBER: 137:185502
TITLE: Preparation of 2,6-disubstituted 7-oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders
INVENTOR(S): Chen, Jian Jeffrey; Dunn, James Patrick; **Goldstein, David Michael**; Stahl, Christoph Martin
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 207 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

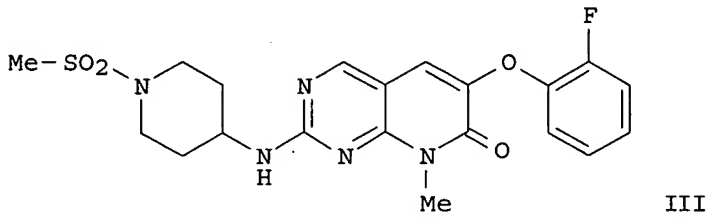
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002064594	A2	20020822	WO 2002-EP1106	20020204

WO 2002064594		A3	20030109			
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW					
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2434834		AA	20020822	CA 2002-2434834		20020204
EP 1361880		A2	20031119	EP 2002-726103		20020204
EP 1361880		B1	20050928			
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2002007172		A	20040330	BR 2002-7172		20020204
CN 1503672		A	20040609	CN 2002-804834		20020204
JP 2004525896		T2	20040826	JP 2002-564525		20020204
NZ 526961		A	20050324	NZ 2002-526961		20020204
AT 305303		E	20051015	AT 2002-726103		20020204
RU 2269527		C2	20060210	RU 2003-125887		20020204
ES 2249574		T3	20060401	ES 2002-2726103		20020204
US 2003171584		A1	20030911	US 2002-73845		20020211
US 6696566		B2	20040224			
ZA 2003005938		A	20041101	ZA 2003-5938		20030731
NO 2003003540		A	20030811	NO 2003-3540		20030811
BG 108085		A	20041230	BG 2003-108085		20030812
US 2004116698		A1	20040617	US 2003-722703		20031125
PRIORITY APPLN. INFO.:				US 2001-268375P	P	20010212
				US 2001-334654P	P	20011130
				WO 2002-EP1106	W	20020204
				US 2002-73845	A1	20020211

OTHER SOURCE(S): MARPAT 137:185502

GI





AB The title compds. with general formula I or II [wherein Z = N or CH; W = NR2; X1 = O, NR4, S, CR5R6, or CO; R4, R5, and R6 = independently H or alkyl; X2 = O or NR7; Ar1 = (hetero)aryl; R2 = H, alkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, heteroalkyl(oxy)carbonyl, or R21-R22; R21 = alkylene or CO; R22 = alkyl or alkoxy; R1 = H, (halo)alkyl,

(hetero)aryl, (hetero)aralkyl, cyclo(alkyl)alkyl, hetero(cyclyl)alkyl, cyanoalkyl, heterocyclyl, or substituted hetero(alkyl)cycloalkyl, heterocycloamino, or acyl(alkylene); R3 = H, (cyclo)alkyl, cycloalkylalkyl, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, acylalkylene, (un)substituted amino; R7 = H or alkyl; R8 and R9 = independently H, (cyclo)alkyl, aryl(sulfonyl), aralkyl, cycloalkylalkyl, heteroalkyl, alkylsulfonyl, acyl, etc.; and pharmaceutically acceptable salts thereof] were prepared For example, the substitution reaction of 6-(2-fluorophenoxy)-8-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one (preparation given) and 1-(methylsulfonyl)piperidin-4-amine (preparation given), followed by salt formation, gave the phenoxypyrido[2,3-d]pyrimidinone III•HCl. I and II have IC50 activity against p38 kinase in the range of 0.1-5000 nM, with the majority being 1-1000 nM. I and II are useful for the treatment of arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease, or Alzheimer's disease (no data).

IC ICM C07D487-04
ICS C07D471-04; C07D519-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST pyridopyrimidine pyridopyrimidinone oxopyridopyrimidine prepn treatment **p38** disorder; pyridopyrimidinone pyridopyrimidine oxopyridopyrimidine prepn Alzheimer disease treatment

IT Inflammation
(Crohn's disease; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT Intestine, disease
(Crohn's; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT Respiratory distress syndrome
(adult; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT Lung, disease
(chronic obstructive pulmonary disease; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT Intestine, disease
(irritable bowel syndrome; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT Alzheimer's disease
Anti-Alzheimer's agents
Antiarthritics
Arthritis
Human
(preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT 449808-64-4P 449809-00-1P 449809-02-3P 449809-18-1P 449809-33-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(inhibitor; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT 449808-60-0P 449808-61-1P 449808-63-3P 449808-65-5P 449808-66-6P
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449811-95-4P 449811-96-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitor; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

IT 6309-59-7P 17277-58-6P 17759-30-7P 17918-67-1P 21926-00-1P
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449811-89-6P 449811-90-9P 449811-91-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of oxopyrido[2,3-d]pyrimidines for treating

p38 mediated disorders)
IT 165245-96-5, **p38** Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)
IT 770-31-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)
IT 62-53-3, Aniline, reactions 64-04-0, Phenethylamine 75-30-9, 2-Iodopropane 78-81-9, Isobutylamine 78-84-2, Isobutyraldehyde 96-32-2, Methyl bromoacetate 98-09-9, Benzenesulfonyl chloride 100-46-9, Benzylamine, reactions 104-10-9, 2-(4-Aminophenyl)ethanol 108-98-5, Thiophenol, reactions 109-55-7, N,N-Dimethylpropane-1,3-diamine 109-73-9, Butylamine, reactions 109-85-3, 2-Methoxyethylamine 123-42-2, 4-Hydroxy-4-methyl2-pentanone 124-68-5, 2-Amino-2-methylpropan-1-ol 367-12-4, 2-Fluorophenol 367-25-9, 2,4-Difluoroaniline 371-40-4, 4-Fluoroaniline 371-41-5, 4-Fluorophenol 501-53-1, Benzyl chloroformate 502-83-0, 2-Amino-4-(methylthio)butan-1-ol 616-30-8, 3-Aminopropane-1,2-diol 765-30-0, Cyclopropylamine 1001-53-2, N-(2-Aminoethyl)acetamide 1003-03-8, Cyclopentylamine 1072-72-6, Tetrahydrothiopyran-4-one 1609-86-5, tert-Butyl isocyanate 1939-99-7, α-Toluenesulfonyl chloride 2026-48-4 2032-34-0, 3,3-Diethoxypropanenitrile 2065-23-8, Methyl phenoxyacetate 2454-96-8, 2-Amino-5-Methylpyridine hydrochloride 2516-47-4, Cyclopropylmethylamine 2941-20-0, α-Ethylbenzylamine 3218-02-8, Cyclohexanemethanamine 3731-51-9, Pyridin-2-ylmethylamine 3731-53-1, 4-(Aminomethyl)pyridine 4244-84-2, Ethyl β-alaninate hydrochloride 4313-56-8 4543-47-9, 3-Furfurylamine 4572-03-6, 1-(3-Aminopropyl)-4-methylpiperazine 4841-22-9, Methyl 4-chlorophenoxyacetate 5332-73-0, 3-Methoxypropylamine 5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate 6126-22-3 6956-85-0, Methyl 2-chlorophenoxyacetate 7116-38-3 7149-62-4 7663-77-6, 1-(3-Aminopropyl)pyrrolidin-2-one 10316-79-7 16369-14-5, 2-Aminopentan-1-ol 16867-03-1, 2-Aminopyridin-3-ol 18944-77-9 20173-24-4, 2-(Pyridin-3-yl)ethylamine 27489-62-9, trans-4-Aminocyclohexanol 27578-60-5, 2-Piperidin-1-ylethylamine 28875-17-4, N-(tert-Butoxycarbonyl)-L-alanine methyl ester 38041-19-9, 4-Aminotetrahydropyran 38519-63-0, 4-(2-Diethylaminoethoxy)aniline 40296-46-6 50541-93-0, 4-Amino-1-benzylpiperidine 58859-46-4, Ethyl 4-amino-1-piperidinecarboxylate 70183-89-0 129368-01-0 138564-16-6 141286-91-1, Methyl 2,6-difluorophenoxyacetate 210240-73-6 215940-92-4 226396-70-9 449811-63-6 449811-69-2 449811-71-6 449811-73-8 449811-75-0 449811-76-1 449811-78-3 449811-79-4 449811-81-8 449811-82-9 449811-84-1 449811-85-2 449811-86-3 449811-87-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of oxopyrido[2,3-d]pyrimidines for treating **p38** mediated disorders)

L47 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:171896 HCAPLUS
DOCUMENT NUMBER: 136:232316
TITLE: 7-Oxopyridopyrimidines as inhibitors of cellular proliferation, and particularly as inhibitors of **p38** kinase, for treatment of **p38** -related conditions
INVENTOR(S): Chen, Jian Jeffrey; Dunn, James Patrick; **Goldstein, David Michael**; Lim, Julie Anne
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

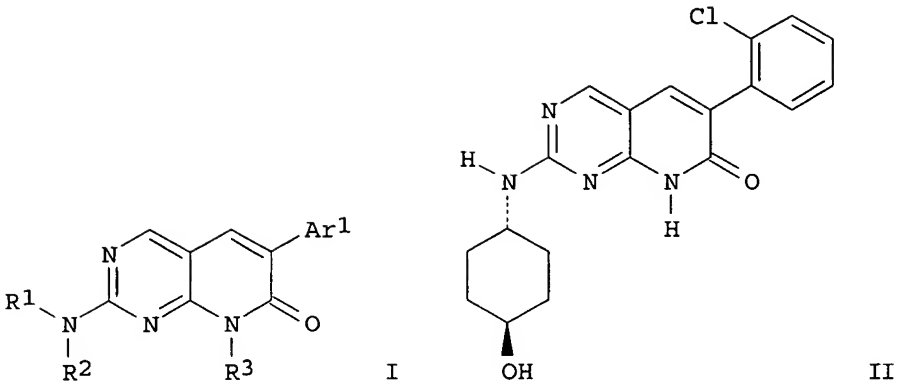
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018380	A1	20020307	WO 2001-EP9689	20010822
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2420286	AA	20020307	CA 2001-2420286	20010822
AU 2001093784	A5	20020313	AU 2001-93784	20010822
EP 1315726	A1	20030604	EP 2001-974206	20010822
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001013628	A	20030701	BR 2001-13628	20010822
JP 2004507541	T2	20040311	JP 2002-523895	20010822
US 2002055513	A1	20020509	US 2001-943338	20010830
US 6518276	B2	20030211		
US 2002137756	A1	20020926	US 2001-943407	20010830
US 6506749	B2	20030114		
US 2003153586	A1	20030814	US 2002-230723	20020829
US 6861423	B2	20050301		
US 2003144307	A1	20030731	US 2002-315633	20021210
US 6753427	B2	20040622		
ZA 2003001079	A	20040507	ZA 2003-1079	20030207
US 2004192709	A1	20040930	US 2004-816554	20040401

PRIORITY APPLN. INFO.:

US 2000-229584P	P	20000831
US 2000-229577P	P	20000831
WO 2001-EP9689	W	20010822
US 2001-943338	A3	20010830
US 2001-943407	A1	20010830
US 2002-315633	A3	20021210

position stones

OTHER SOURCE(S): MARPAT 136:232316
GI



AB Compds. I are disclosed [wherein: R1 = H or alkyl; R2 = substituted cycloalkyl, hetero-substituted cycloalkyl, heteroalkyl-substituted cycloalkyl, hetero-substituted cycloalkyl-aryl, heterocyclyl, heterocyclylspirocycloalkyl, aralkoxy, alkoxy, -alkylene-S(O)n-alkyl (where n = 1 or 2) or SO2Ar2; R3 = H, amino, monoalkylamino, dialkylamino, acylamino, NRaC(:O)Rb (where Ra = H or alkyl, and Rb = heterocyclyl or heteroalkyl), alkyl, cycloalkyl, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, -alkylene-C(O)R (where R = H, alkyl, OH, alkoxy, amino, monoalkylamino or dialkylamino), acyl, or phthalimidoalkyl; and each of Ar1 and Ar2 = aryl]. Also disclosed in claims is their use for treatment of disorders selected from the group consisting of arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease. A list of 151 compds. I is given, as well as approx. 100 synthetic examples. For instance, cyclocondensation of 4-amino-2-(methylthio)pyrimidine-5-carboxaldehyde with Et (2-chlorophenyl)acetate, followed by oxidation of the sulfide to a sulfone with Oxone, and displacement of the Me sulfone with trans-4-aminocyclohexanol, gave 78% title compound II. In an in vitro p38 assay, I had IC50 values ranging from about 4.76 μM to about 0.0003 μM.

IC ICM C07D471-04
ICS A61K031-519; A61P031-00; A61P029-00; C07D471-04; C07D239-00; C07D221-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST oxopyridopyrimidine prepn **p38** kinase inhibitor; pyridopyrimidine prepn inhibitor cellular proliferation

IT Inflammation
(Crohn's disease, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT Intestine, disease
(Crohn's, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT Respiratory distress syndrome
(adult, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT Lung, disease
(chronic obstructive pulmonary disease, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of production; preparation of oxopyridopyrimidines as **p38**

kinase inhibitors)

IT Intestine, disease
(irritable bowel syndrome, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Cytotoxic agents
(preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT 402928-12-5P
RL: BYP (Byproduct); PREP (Preparation)
(byproduct; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT 402927-35-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT 402740-32-3P 402740-60-7P 402740-62-9P 402740-64-1P 402925-68-2P
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of oxopyridopyrimidines as **p38** kinase

inhibitors)

IT 383-50-6P, 2-Fluoroethyl tosylate 588-36-3P, 4-Amino-2-(methylthio)pyrimidine-5-methanol 770-31-0P, 4-Amino-2-(methylthio)pyrimidine-5-carboxaldehyde 776-53-4P, Ethyl 4-amino-2-(methylthio)pyrimidine-5-carboxylate 2251-06-1P, Ethyl 4-[(4-fluorophenyl)amino]-2-(methylthio)pyrimidine-5-carboxylate 6309-59-7P, Tetrahydrothiopyran-4-one oxime 17759-30-7P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-methanol 21926-00-1P, 4-Aminotetrahydrothiopyran 61224-82-6P, 4-(Ethylsulfanyl)butan-2-one 76360-82-2P, Ethyl 4-(methylamino)-2-(methylthio)pyrimidine-5-carboxylate 97181-50-5P, 4-(Trifluoroacetamido)-1-benzylpiperidine 97181-51-6P, 4-(Trifluoroacetamido)piperidine 102669-01-2P 105161-35-1P, 4-Amino-2-sulfanylpyrimidine-5-carboxaldehyde 119712-80-0P, 4-(Ethylsulfanyl)butan-2-one oxime 161124-03-4P, 4-Fluoro-2-(methylthio)pyrimidine 182223-53-6P, Benzyl (1-benzylpiperidin-4-yl)carbamate 182223-54-7P, Benzyl piperidin-4-ylcarbamate 185040-32-8P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-carboxaldehyde 187217-99-8P, 4-Amino-1-(2,2,2-trifluoroethyl)piperidine 210240-20-3P 211247-46-0P, 4-(Cyclopropylamino)-5-formyl-2-(methylthio)pyrimidine 335653-59-3P, 4-(N-BOC-amino)-1-(2,2,2-trifluoroethyl)piperidine 402740-25-4P 402740-26-5P, 6-(2-Chlorophenyl)-2-(methanesulfonyl)pyrido[2,3-d]pyrimidin-7-ol 402740-43-6P 402740-45-8P, 6-(2-Chlorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7-ol 402740-85-6P 402927-64-4P 402927-65-5P 402927-66-6P 402927-67-7P 402927-68-8P 402927-69-9P 402927-70-2P 402927-71-3P 402927-72-4P 402927-73-5P 402927-74-6P 402927-75-7P, N-(2-Cyanoethyl)-4-aminopiperidine 402927-76-8P 402927-77-9P 402927-78-0P 402927-79-1P 402927-80-4P 402927-81-5P 402927-82-6P 402927-83-7P 402927-84-8P 402927-85-9P 402927-86-0P 402927-87-1P 402927-88-2P 402927-89-3P 402927-90-6P, 4-[(4-Fluorophenyl)amino]-2-(methylthio)pyrimidine-5-methanol 402927-91-7P, 4-[(4-Fluorophenyl)amino]-2-(methylthio)pyrimidine-5-carboxaldehyde 402927-92-8P 402927-93-9P 402927-94-0P 402927-95-1P 402927-96-2P, Benzyl [1-(methylsulfonyl)piperidin-4-yl]carbamate 402927-97-3P, 1-(Methylsulfonyl)piperidin-4-amine 402927-98-4P 402927-99-5P 402928-00-1P 402928-01-2P 402928-02-3P 402928-03-4P 402928-04-5P 402928-05-6P 402928-06-7P 402928-07-8P 402928-08-9P 402928-09-0P, 2-Amino-4-(ethylsulfanyl)butane

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT 75-08-1, Ethanethiol 78-84-2, Isobutyraldehyde 78-94-4, Methyl vinyl ketone, reactions 96-30-0, 2-Chloro-N-methylacetamide 96-32-2, Methyl bromoacetate 98-59-9, p-Toluenesulfonyl chloride 100-39-0, Benzyl bromide 107-13-1, Acrylonitrile, reactions 115-77-5, 1,1,1-Tris(hydroxymethyl)ethanol, reactions 371-40-4, 4-Fluoroaniline 371-62-0, 2-Fluoroethanol 501-53-1, Benzyl chloroformate 504-63-2, 1,3-Propanediol 558-30-5, Isobutylene oxide 765-30-0, Cyclopropylamine 1072-72-6, Tetrahydrothiopyran-4-one 1129-26-6, 4-Methoxybenzenesulfonamide 2032-34-0, 3,3-Diethoxypropanenitrile 2615-25-0, trans-1,4-Diaminocyclohexane 2675-89-0, 2-Chloro-N,N-dimethylacetamide 3680-02-2, Methyl vinyl sulfone 3891-07-4, N-(2-Hydroxyethyl)phthalimide 4313-56-8 4319-49-7, 4-Aminomorpholine 4704-94-3, 2-(Hydroxymethyl)-1,3-propanediol 5909-24-0, Ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate 6338-70-1, Tetrahydro-3-thiopheneamine 1,1-dioxide 10316-79-7, (1-(Hydroxymethyl)cyclopentyl)amine 15159-40-7, 4-Morpholinecarbonyl chloride 15827-56-2, cis-1,4-Diaminocyclohexane 27489-62-9, trans-4-Aminocyclohexanol 36768-62-4, 4-Amino-2,2,6,6-

tetramethylpiperidine 38041-19-9, 4-Aminotetrahydropyran 40061-54-9, Ethyl (2-chlorophenyl)acetate 40525-78-8, cis-4-Aminocyclohexanol 49844-90-8, 4-Chloro-2-(methylthio)pyrimidine 50541-93-0, 4-Amino-1-benzylpiperidine 51498-33-0, Ethyl 4-aminocyclohexanecarboxylate 58859-46-4, Ethyl 4-aminopiperidine-1-carboxylate 73874-95-0 76513-69-4, 2-(Trimethylsilyl)ethoxymethyl chloride 89854-94-4 93550-77-7, (2-Iodoethoxy)triisopropylsilane 97096-16-7, (1,4-Dioxaspiro[4.5]dec-8-yl)amine 99724-19-3 111705-51-2, (S)-3-(N-Tritylamino)tetrahydrofuran 164646-07-5, 4-(Aminomethyl)cyclohexanol 402928-10-3 402928-11-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(precursor; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

IT 165245-96-5, **p-38** Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of oxopyridopyrimidines as **p38** kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

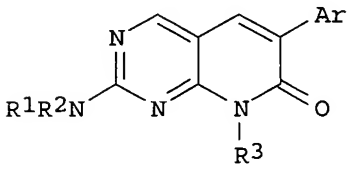
L47 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:171895 HCAPLUS
DOCUMENT NUMBER: 136:216763
TITLE: Preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors
INVENTOR(S): Arzeno, Humberto Bartolome; Chen, Jian Jeffrey; Dunn, James Patrick; **Goldstein, David Michael**; Lim, Julie Anne
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018379	A2	20020307	WO 2001-EP9688	20010822
WO 2002018379	A3	20020725		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2420122	AA	20020307	CA 2001-2420122	20010822
AU 2002012147	A5	20020313	AU 2002-12147	20010822
EP 1315727	A2	20030604	EP 2001-980258	20010822
EP 1315727	B1	20050629		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001013590	A	20030722	BR 2001-13590	20010822
JP 2004507540	T2	20040311	JP 2002-523894	20010822
AT 298751	E	20050715	AT 2001-980258	20010822
ES 2243568	T3	20051201	ES 2001-1980258	20010822
CN 1721412	A	20060118	CN 2005-10083529	20010822
US 2002055513	A1	20020509	US 2001-943338	20010830

US 6518276	B2	20030211			
US 2003153586	A1	20030814	US 2002-230723		20020829
US 6861423	B2	20050301			
US 2003144307	A1	20030731	US 2002-315633		20021210
US 6753427	B2	20040622			
ZA 2003001078	A	20040507	ZA 2003-1078		20030207
US 2004192709	A1	20040930	US 2004-816554		20040401
PRIORITY APPLN. INFO.:			US 2000-229577P	P	20000831
			US 2000-229584P	P	20000831
			CN 2001-815027	A3	20010822
			WO 2001-EP9688	W	20010822
			US 2001-943338	A3	20010830
			US 2001-943407	A1	20010830
			US 2002-315633	A3	20021210

OTHER SOURCE(S): MARPAT 136:216763

GI



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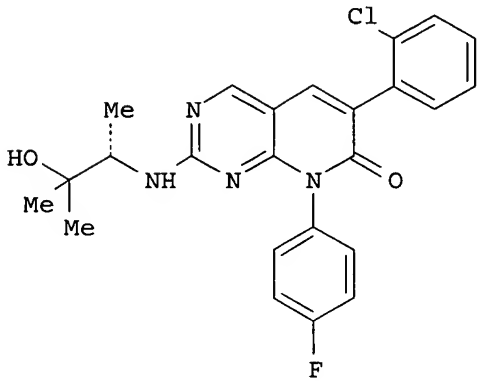


II

AB The present invention provides compds. of the formula I [R1 = H, alkyl; R2 = alkoxy-substituted alkyl, heterocyclyl, cycloalkyl; etc.; R1R2 = heterocyclyl; R3 = H, alkyl, amino, aryl, acyl, etc.; Ar = aryl], a prodrug or a pharmaceutically acceptable salt thereof, and processes for their preparation and their use for the treatment of p38 mediated disorders. Thus, II was prepared and inhibited p38 MAP kinase in vitro with IC50 of 0.0003 μM.

IC ICM C07D471-04
ICS A61K031-519; A61P025-00; C07D239-46; C07D471-04; C07D239-00; C07D221-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST oxopyridopyrimidine prepn **p38** MAP kinase inhibitor; pyridopyrimidine oxo prepn **p38** MAP kinase inhibitor

IT Inflammation
(Crohn's disease, treatment; preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Intestine, disease
(Crohn's, treatment; preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Respiratory distress syndrome
(adult, treatment; preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Lung, disease
(chronic obstructive pulmonary disease, treatment; preparation of

7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Intestine, disease
(irritable bowel syndrome, treatment; preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Human
(preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT 165245-96-5, **p38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT 402740-27-6P 402740-28-7P 402740-29-8P 402740-30-1P 402740-31-2P
402740-32-3P 402740-33-4P 402740-34-5P 402740-35-6P 402740-36-7P
402740-37-8P 402740-38-9P 402740-39-0P 402740-40-3P 402740-41-4P
402740-42-5P 402740-56-1P 402740-57-2P 402740-58-3P 402740-59-4P
402740-60-7P 402740-61-8P 402740-62-9P 402740-63-0P 402740-64-1P
402740-65-2P 402740-66-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT 115-69-5 115-70-8 534-03-2, Serinol 683-57-8, 2-Bromoacetamide
2026-48-4 2032-34-0 2675-89-0, 2-Chloro-N,N-dimethylacetamide
2749-11-3 5292-43-3, tert-Butyl bromoacetate 5856-62-2 5909-24-0
7149-42-0 24629-25-2, (S)-Isoleucinol 40061-54-9, Ethyl (2-chlorophenyl)acetate 53448-09-2, (R)-Leucinol 74608-26-7
112245-13-3, (S)-tert-Leucinol 132431-09-5 402740-85-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT 588-36-3P 770-31-0P 776-53-4P 17759-30-7P 76360-82-2P
102669-01-2P 105161-35-1P 180532-43-8P 185040-32-8P 402740-25-4P
402740-26-5P 402740-43-6P 402740-45-8P 402740-46-9P 402740-47-0P
402740-48-1P 402740-49-2P 402740-51-6P 402740-54-9P 402740-55-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

L47 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:618153 HCAPLUS
TITLE: 4-Azaindoles: Novel inhibitors of **p38** MAP kinase
AUTHOR(S): Trejo, Alejandra; Arzeno, Humberto; Browner, Michelle; Cheng, Soan; Comer, Daniel D.; Dalrymple, Stacie; Freire-Moar, Jose; Lim, Julie; McIntosh, Joel; Miller, Jennifer; Myers, Peter L.; Saunders, John; Sjogren, Eric B.; Spellmyer, David; Warren, Stephen D.; Whiteley, Phyllis E.; Zeng, Lu; **Goldstein, David M.**
CORPORATE SOURCE: Roche Bioscience, Palo Alto, CA, 94304, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-302. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Regulation of cytokine biosynthesis in various cell types is regulated through activation of p38 MAP kinase including the proinflammatory cytokines interleukin 1β (IL-1β) and tumor necrosis factorα (TNFα). Anti IL-1ra and TNFα biologics such as Kineret, Infliximab and Etanercept have clin. validated that modulation of theses cytokines leads to dramatic improvement in inflammatory diseases such as rheumatoid arthritis and Crohn's disease. Development of an orally active small mol. inhibitor of p38 is of extreme interest and focus of many pharmaceutical research programs. Initial approaches towards developing novel proprietary leads in the p38 program lead to the synthesis of compds. in the 4-azaindole class which are extremely potent with IC 50's in the low nanomolar range. Synthesis of these compds. along with their biol. activity will be presented.

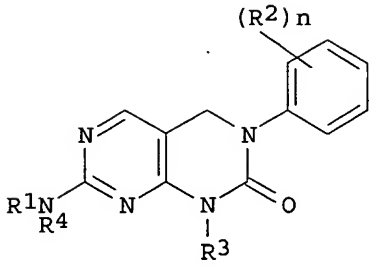
L47 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:300721 HCAPLUS
DOCUMENT NUMBER: 134:326540
TITLE: Preparation of alkylamino substituted bicyclic nitrogen heterocycles for pharmaceutical use as inhibitors of **p38** protein kinase
INVENTOR(S): Dunn, James Patrick; Fisher, Lawrence Emerson; **Goldstein, David Michael**; Harris, William; Hill, Christopher Huw; Smith, Ian Edward David; Welch, Teresa Rosanne
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 177 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001029042	A1	20010426	WO 2000-EP10088		20001013
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2388142	AA	20010426	CA 2000-2388142		20001013
BR 2000015243	A	20020716	BR 2000-15243		20001013
EP 1228070	A1	20020807	EP 2000-967864		20001013
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
TR 200201057	T2	20020923	TR 2002-1057		20001013
JP 2003512378	T2	20030402	JP 2001-531840		20001013
NZ 518119	A	20040227	NZ 2000-518119		20001013
AU 776250	B2	20040902	AU 2000-77873		20001013
RU 2265606	C2	20051210	RU 2002-112753		20001013
US 6451804	B1	20020917	US 2000-693337		20001020
ZA 2002002540	A	20030630	ZA 2002-2540		20020328
NO 2002001781	A	20020418	NO 2002-1781		20020416
HK 1051039	A1	20050401	HK 2003-103208		20030506
PRIORITY APPLN. INFO.:			US 1999-160803P	P	19991021
			US 2000-213743P	P	20000622

WO 2000-EP10088 W 20001013

OTHER SOURCE(S): MARPAT 134:326540

GI



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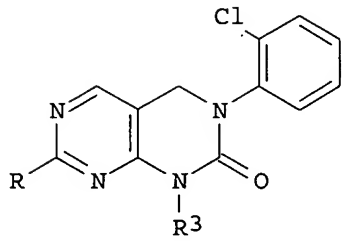


II

AB Alkylamino-substituted dihydropyrimido[4,5-d]pyrimidinone derivs., such as I [R1 = H, alkyl, alkenyl, alkynyl, acyl, cycloalkyl, etc.; R2 = vinyl, alkyl, halogen, heteroalkyl; R3 = alkyl, heteroalkyl, cycloalkyl, heterocyclyl, etc.; R4 = H, alkyl, etc.; n = 0-3], were prepared for pharmaceutical use. The compds. are p38 inhibitors and may be used in the treatment of arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease, osteoporosis, or Alzheimer's disease. Thus, dihydropyrimido[4,5-d]pyrimidinone II (R = NHCMe2CH2OH, R3 = Me) was prepared via a substitution reaction of H2NCMe2CH2OH with sulfone II (R = SO2Me, R3 = Me) when combined and heated to 100-110° for 1 h. The prepared dihydropyrimido[4,5-d]pyrimidinone derivs. showed 50% p38 inhibitory activity at concns. < 10 μM.

IC ICM C07D487-04
ICS A61K031-505; A61P029-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7, 63

IT Anti-inflammatory agents
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 335651-19-9P 335651-20-2P 335651-24-6P 335651-30-4P 335651-49-5P
335651-50-8P 335651-51-9P 335651-53-1P 335651-55-3P 335651-56-4P
335651-57-5P 335651-58-6P 335651-59-7P 335651-60-0P 335651-61-1P
335651-62-2P 335651-63-3P 335651-64-4P 335651-65-5P 335651-66-6P
335651-67-7P 335651-69-9P 335651-77-9P 335651-88-2P 335651-89-3P
335651-93-9P 335651-94-0P 335651-95-1P 335651-96-2P 335651-97-3P
335651-98-4P 335651-99-5P 335652-00-1P 335652-06-7P 335652-11-4P
335652-12-5P 335652-13-6P 335652-14-7P 335652-16-9P 335652-18-1P
335652-22-7P 335652-24-9P 335652-26-1P 335652-30-7P 335652-32-9P
335652-36-3P 335652-39-6P 335652-40-9P 335652-41-0P 335652-44-3P
335652-46-5P 335652-47-6P 335652-48-7P 335652-50-1P 335652-55-6P
335652-56-7P 335652-58-9P 335652-59-0P 335652-60-3P 335652-61-4P
335652-62-5P 335652-63-6P 335652-64-7P 335652-65-8P 335652-66-9P
335652-67-0P 335652-68-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 335651-18-8P 335651-21-3P 335651-22-4P 335651-23-5P 335651-25-7P
335651-26-8P 335651-27-9P 335651-28-0P 335651-29-1P 335651-31-5P

335651-32-6P 335651-33-7P 335651-34-8P 335651-36-0P 335651-37-1P
335651-38-2P 335651-39-3P 335651-40-6P 335651-41-7P 335651-42-8P
335651-43-9P 335651-44-0P 335651-45-1P 335651-46-2P 335651-47-3P
335651-48-4P 335651-52-0P 335651-54-2P 335651-68-8P 335651-70-2P
335651-71-3P 335651-72-4P 335651-73-5P 335651-74-6P 335651-75-7P
335651-76-8P 335651-78-0P 335651-79-1P 335651-80-4P 335651-81-5P
335651-82-6P 335651-83-7P 335651-84-8P 335651-85-9P 335651-86-0P
335651-87-1P 335651-90-6P 335651-91-7P 335651-92-8P 335652-02-3P
335652-04-5P 335652-08-9P 335652-10-3P 335652-20-5P 335652-28-3P
335652-34-1P 335652-37-4P 335652-38-5P 335652-42-1P 335652-43-2P
335652-45-4P 335652-49-8P 335652-51-2P 335652-52-3P 335652-53-4P
335652-54-5P 335652-57-8P 335652-69-2P 335652-70-5P 335652-71-6P
335652-72-7P 335652-73-8P 335652-74-9P 335652-75-0P 335652-76-1P
335652-77-2P 335652-78-3P 335652-79-4P 335652-80-7P 335652-81-8P
335652-82-9P 335652-83-0P 335652-84-1P 335652-85-2P 335652-86-3P
335652-87-4P 335652-88-5P 335652-90-9P 335652-91-0P 335652-92-1P
335652-93-2P 335652-94-3P 335652-95-4P 335652-96-5P 335652-97-6P
335652-98-7P 335652-99-8P 335653-00-4P 335653-01-5P 335653-02-6P
335653-03-7P 335653-04-8P 335653-05-9P 335653-06-0P 335653-07-1P
335653-08-2P 335653-09-3P 335653-10-6P 335653-11-7P 335653-12-8P
335653-13-9P 335653-16-2P 335653-17-3P 335653-18-4P 335653-19-5P
335653-20-8P 335653-21-9P 335653-22-0P 335653-23-1P 335653-24-2P
335653-25-3P 335653-26-4P 335653-27-5P 335653-28-6P 335653-29-7P
335653-30-0P 335653-31-1P 335653-32-2P 335653-33-3P 335653-34-4P
335653-35-5P 335653-36-6P 335653-37-7P 335653-38-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 165245-96-5, **p38** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 62-53-3, Benzenamine, reactions 77-85-0 78-96-6 94-05-3 95-51-2
95-53-4, reactions 96-32-2 96-33-3 100-37-8 100-39-0 103-49-1
105-36-2 106-52-5 107-13-1, 2-Propenenitrile, reactions 108-01-0
115-69-5 124-68-5 540-51-2 556-82-1 590-17-0 608-31-1 614-68-6
624-75-9 683-57-8 770-31-0 2615-25-0 2675-89-0 2749-11-3
2955-88-6, 1-Pyrrolidineethanol 3320-83-0 4043-59-8 4313-56-8
4746-97-8, 1,4-Dioxaspiro[4.5]decan-8-one 5271-38-5 5292-43-3
5303-65-1 5909-24-0 6168-72-5 6482-24-2 10316-79-7 13360-57-1
19059-68-8 23735-43-5 25236-64-0 27489-62-9 29943-42-8
35320-23-1 40525-78-8 50541-93-0 58859-46-4 73579-08-5
73874-95-0 76513-69-4 89854-94-4 106268-97-7 108102-48-3
109384-19-2 132431-09-5 144222-22-0 164646-07-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 774-07-2P 776-53-4P 7149-62-4P 17759-30-7P 18511-56-3P
38041-19-9P 61128-73-2P 76360-82-2P 97096-16-7P,
1,4-Dioxaspiro[4.5]decan-8-amine 100193-64-4P 106475-47-2P
138876-37-6P 180918-12-1P 185040-32-8P 187217-99-8P 211245-55-5P
211245-56-6P 266313-81-9P 266313-82-0P 266313-83-1P 266313-84-2P
266315-45-1P 335318-13-3P 335318-14-4P 335318-20-2P 335318-29-1P
335318-30-4P 335653-39-9P 335653-40-2P 335653-41-3P 335653-42-4P
335653-43-5P 335653-44-6P 335653-45-7P 335653-46-8P 335653-47-9P
335653-48-0P 335653-49-1P 335653-50-4P 335653-51-5P 335653-52-6P
335653-53-7P 335653-54-8P 335653-55-9P 335653-56-0P 335653-57-1P

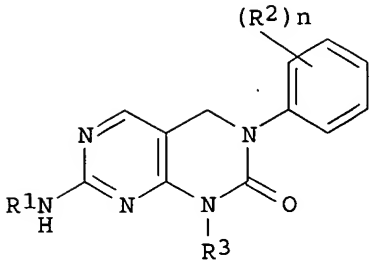
335653-58-2P 335653-59-3P 335653-60-6P 335653-61-7P 335653-62-8P
335653-63-9P 335653-64-0P 335653-65-1P 335653-66-2P 335653-67-3P
335653-68-4P 335653-69-5P 335653-70-8P 335653-71-9P 335653-72-0P
335653-73-1P 335653-74-2P 335653-75-3P 335653-76-4P 335653-77-5P
335653-78-6P 335653-79-7P 335653-80-0P 335653-81-1P 335653-82-2P
335653-83-3P 335653-84-4P 335653-85-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

No

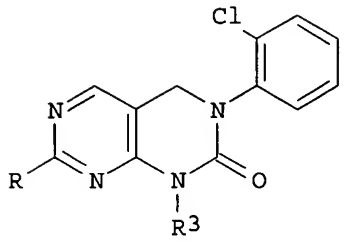
L47 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:300720 HCAPLUS
DOCUMENT NUMBER: 134:311223
TITLE: Preparation of alkylamino substituted bicyclic nitrogen heterocycles for pharmaceutical use as inhibitors of **p38** protein kinase
INVENTOR(S): Dunn, James Patrick; **Goldstein, David Michael**; Harris, William; Smith, Ian Edward David; Welch, Teresa Rosanne
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001029041	A1	20010426	WO 2000-EP10077		20001013
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2388140	AA	20010426	CA 2000-2388140		20001013
BR 2000014973	A	20020716	BR 2000-14973		20001013
TR 200201058	T2	20020722	TR 2002-1058		20001013
EP 1226144	A1	20020731	EP 2000-972755		20001013
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
JP 2003512377	T2	20030402	JP 2001-531839		20001013
AU 776695	B2	20040916	AU 2001-11375		20001013
RU 2264404	C2	20051120	RU 2002-110286		20001013
US 6642241	B1	20031104	US 2000-693364		20001020
ZA 2002002603	A	20030703	ZA 2002-2603		20020403
NO 2002001783	A	20020416	NO 2002-1783		20020416
HK 1051040	A1	20050128	HK 2003-103209		20030506
PRIORITY APPLN. INFO.:			US 1999-160804P	P	19991021
			US 2000-213718P	P	20000622
			WO 2000-EP10077	W	20001013

OTHER SOURCE(S): MARPAT 134:311223
GI



I



II

AB Alkylamino-substituted dihydropyrimido[4,5-d]pyrimidinone derivs., such as I [R1 = H, alkyl, alkenyl, alkynyl, acyl, cycloalkyl, etc.; R2 = vinyl, alkyl, halogen, heteroalkyl; R3 = alkyl, heteroalkyl, cycloalkyl, heterocyclyl, etc.; n = 0-3], were prepared for pharmaceutical use as inhibitors of p38 protein kinase for the treatment of conditions such as arthritis, Crohn's disease, obstructive pulmonary disease, or irritable bowel syndrome.. Thus, dihydropyrimido[4,5-d]pyrimidinone II (R = NHCHMe2, R3 = CH2CO2H) was prepared via a substitution reaction of H2NCHMe2 with sulfone II (R = SO2CH2Ph, R3 = CH2CO2Et) when combined and heated to 90-100° for 1 h. The prepared dihydropyrimido[4,5-d]pyrimidinone derivs. showed p38 50% inhibitory activity at concns. < 10 μM.

IC ICM C07D487-04
ICS A61K031-505; A61P029-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7, 63

IT Anti-inflammatory agents
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 335318-15-5P 335318-19-9P 335318-22-4P 335318-39-3P 335318-40-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 335318-09-7P 335318-10-0P 335318-11-1P 335318-12-2P 335318-16-6P
335318-17-7P 335318-18-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 165245-96-5, **P38** Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

IT 62-56-6, Thiourea, reactions 75-31-0, 2-Propanamine, reactions 94-05-3
95-51-2 100-39-0 105-36-2 109-86-4 3040-44-6, 1-Piperidineethanol
5271-38-5 23735-43-5 23788-74-1 93550-77-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)

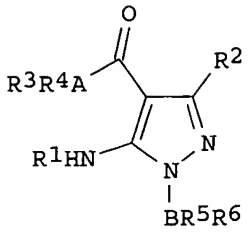
IT 774-07-2P 7149-62-4P 100193-64-4P 335318-13-3P 335318-14-4P
335318-20-2P 335318-21-3P 335318-23-5P 335318-24-6P 335318-25-7P
335318-26-8P 335318-27-9P 335318-29-1P 335318-30-4P 335318-31-5P

335318-32-6P 335318-33-7P 335318-34-8P 335318-35-9P 335318-36-0P
335318-37-1P 335318-38-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of **p38** protein kinase)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:228861 HCAPLUS
DOCUMENT NUMBER: 134:266303
TITLE: Preparation of 5-amino-4-aroyl-1-arylpyrazoles as **p-38** MAP kinase inhibitors.
INVENTOR(S): **Goldstein, David Michael**; Labadie, Sharada Shenvi; Rotstein, David Mark; Sjogren, Eric Brian; Talamas, Francisco Xavier
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021591	A1	20010329	WO 2000-EP8981	20000914
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6316466	B1	20011113	US 1999-401141	19990922
CA 2385447	AA	20010329	CA 2000-2385447	20000914
BR 2000014225	A	20020521	BR 2000-14225	20000914
EP 1218346	A1	20020703	EP 2000-966008	20000914
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003509495	T2	20030311	JP 2001-524971	20000914
AU 777470	B2	20041021	AU 2000-76558	20000914
PRIORITY APPLN. INFO.:			US 1999-401141 A	19990922
			US 1998-84250P P	19980505
			US 1999-122410P P	19990302
			US 1999-130369P P	19990421
			US 1999-305737 A2	19990505
			WO 2000-EP8981 W	20000914

OTHER SOURCE(S): MARPAT 134:266303
GI



I

AB Title compds. [I; R1 = H, acyl; A, B = aryl, heteroaryl; R3 = amino, acylamino, (substituted) heterocyclyl, aryl, heteroaryl, heteroalkyl, etc.; R4 = H, halo, alkyl, alkoxy, OH; R5 = H, halo, alkyl, haloalkyl, OH, amino, thioalkyl, heteroalkyl, (substituted) heterocyclyl, etc.; R6 = H, halo, alkyl, alkoxy], were prepared Thus, 5-amino-4-(3-bromobenzoyl)-1-(4-fluorophenyl)pyrazole (preparation given), 4-(2-propynyl)morpholine (preparation given), (PPh3)2PdCl2, and CuI were heated in diisopropylamine at 70° for 10 h to give 5-amino-1-(4-fluorophenyl)-4-[3-(3-morpholin-4-ylprop-1-ynyl)benzoyl]pyrazole hydrochloride. Tested I inhibited LPS-induced TNFα production in THP1 cells with IC50 = 0.17-1.77 μM.

IC ICM C07D231-38
ICS C07D413-10; C07D403-10; C07D401-10; C07D413-12; C07D401-12; C07D409-06; C07D405-06; C07D401-06; C07D405-12; A61K031-415; C07D413-10; C07D265-00; C07D231-00; C07D403-10; C07D241-00; C07D231-00

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT Anti-inflammatory agents
Antiarthritics
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(production inhibitors; preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 165245-96-5, **p-38** MAP kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibitors; preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 249935-56-6P 249935-63-5P 249935-94-2P 249936-51-4P 249936-54-7P 249936-65-0P 249937-47-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 249935-54-4P 249935-55-5P 249935-57-7P 249935-58-8P 249935-59-9P
249935-60-2P 249935-61-3P 249935-62-4P 249935-64-6P 249935-66-8P
249935-67-9P 249935-68-0P 249935-69-1P 249935-70-4P 249935-71-5P
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249935-98-6P 249935-99-7P 249936-00-3P 249936-01-4P 249936-02-5P
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249936-08-1P 249936-09-2P 249936-10-5P 249936-11-6P 249936-12-7P
249936-13-8P 249936-14-9P 249936-15-0P 249936-16-1P 249936-17-2P
249936-18-3P 249936-19-4P 249936-20-7P 249936-21-8P 249936-22-9P
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331777-29-8P 331777-30-1P 331777-31-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 74-89-5, Methylamine, reactions 75-05-8, Acetonitrile, reactions 79-14-1, Glycolic acid, reactions 79-22-1, Methyl chloroformate 94-05-3, Ethyl ethoxymethylenecyanoacetate 100-63-0, Phenylhydrazine 106-96-7, Propargyl bromide 109-01-3, N-Methylpiperazine 109-70-6, 1-Bromo-3-chloropropane 109-89-7, Diethylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 111-42-2, Diethanolamine, reactions 111-95-5 124-40-3, Dimethylamine, reactions 141-43-5, 2-Aminoethanol, reactions 371-14-2, 4-Fluorophenylhydrazine 462-08-8, 3-Aminopyridine 504-29-0, 2-Aminopyridine 504-30-3, 3(2H)-Pyridazinone 540-51-2, 2-Bromoethanol 586-98-1, 2-Pyridinemethanol 614-16-4, Benzoylacetonitrile 615-00-9, 2,4-Dimethylphenylhydrazine 618-91-7, Methyl 3-iodobenzoate 626-55-1, 3-Bromopyridine 658-27-5, 3-Fluorophenylhydrazine 693-98-1, 2-Methylimidazole 822-36-6, 4-Methylimidazole 877-66-7, 4-Methylsulfonylphenylhydrazine 1711-09-7 1795-48-8, Isopropyl isocyanate 1820-80-0, 3-Aminopyrazole 1878-67-7, 3-Bromophenylacetic acid 2127-03-9, 2-Aldrithiol 2339-53-9, 3-Fluoro-6-methylphenylhydrazine 2386-58-5, Vinyl sulfonamide 2398-37-0, 3-Bromoanisole 2402-97-3, 3-Bromopyridine N-oxide 3445-11-2 3471-32-7, 4-Methoxyphenylhydrazine 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 5292-43-3, tert-Butyl bromoacetate 5382-16-1, 4-Hydroxypiperidine 7486-35-3, Vinyltributyltin 18312-46-4, 2-Methoxyphenylhydrazine 19275-55-9, 2-Ethylphenylhydrazine 19438-10-9, Methyl 3-hydroxybenzoate 23788-74-1 51304-65-5, 3-Chloro-4-methylphenylhydrazine 51934-41-9, Ethyl 4-iodobenzoate 58791-94-9 63693-65-2, 4-Isopropylphenylhydrazine 97674-02-7, Tributyl(1-ethoxyvinyl)tin 124252-41-1 131534-65-1, Pyridine-3-boronic acid, 1,3-propanediol cyclic ester 249937-03-9 249937-48-2 331777-17-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

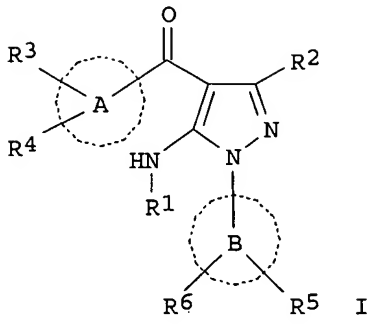
IT 5799-76-8P 21667-64-1P 28229-69-8P 70591-86-5P 79601-27-7P
138907-68-3P 183158-31-8P 187949-90-2P 247206-80-0P 249936-98-9P
249936-99-0P 249937-00-6P 249937-02-8P 249937-05-1P 249937-06-2P
249937-07-3P 249937-08-4P 249937-09-5P 249937-10-8P 249937-11-9P
249937-12-0P 249937-13-1P 249937-16-4P 249937-18-6P 249937-21-1P
249937-22-2P 249937-25-5P 249937-44-8P 249937-45-9P 331777-15-2P
331777-16-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:830885 HCAPLUS
DOCUMENT NUMBER: 135:357921
TITLE: Preparation of 5-amino-4-aroyl-1-arylpyrazoles as **p-38** MAP kinase inhibitors.
INVENTOR(S): **Goldstein, David Michael**; Labadie, Sharada Shenvi; Rotstein, David Mark; Sjogren, Eric Brian; Talamas, Francisco Xavier
PATENT ASSIGNEE(S): Syntex (U.S.A.) Llc, USA
SOURCE: U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 305,737.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6316466	B1	20011113	US 1999-401141		19990922
US 6376527	B1	20020423	US 1999-305737		19990505
CA 2385447	AA	20010329	CA 2000-2385447		20000914
WO 2001021591	A1	20010329	WO 2000-EP8981		20000914
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
BR 2000014225	A	20020521	BR 2000-14225		20000914
TR 200200778	T2	20020621	TR 2002-778		20000914
EP 1218346	A1	20020703	EP 2000-966008		20000914
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
JP 2003509495	T2	20030311	JP 2001-524971		20000914
AU 777470	B2	20041021	AU 2000-76558		20000914
ZA 2000006272	A	20020204	ZA 2000-6272		20001102
US 2002103245	A1	20020801	US 2001-909966		20010719
US 6444696	B2	20020903			
US 2002156114	A1	20021024	US 2002-45903		20020111
US 2003018051	A1	20030123	US 2002-66040		20020201
US 6979693	B2	20051227			
ZA 2002001559	A	20030526	ZA 2002-1559		20020225
PRIORITY APPLN. INFO.:			US 1998-84250P	P	19980505
			US 1999-122410P	P	19990302

US 1999-130369P	P	19990421
US 1999-305737	A2	19990505
US 1999-401141	A	19990922
WO 2000-EP8981	W	20000914

OTHER SOURCE(S): MARPAT 135:357921
GI



I

AB Title compds. [I; R1 = H, acyl; R2 = H, alkyl; A, B = aryl, heteroaryl; R3 = amino, acylamino, (substituted) heterocyclyl, aryl, heteroaryl, heteroalkyl, etc.; R4 = H, halo, alkyl, alkoxy, OH; R5 = H, halo, alkyl, haloalkyl, OH, amino, etc.; R6 = H, halo, alkyl, alkoxy], were prepared and formulated. Thus, 5-amino-4-(3-bromobenzoyl)-1-(4-fluorophenyl)pyrazole (preparation given), 4-(2-propynyl)morpholine (preparation given), (PPh3)2PdCl2, and CuI were heated in diisopropylamine at 70° for 10 h to give 5-amino-1-(4-fluorophenyl)-4-[3-(3-morpholin-4-ylprop-1-ynyl)benzoyl]pyrazole hydrochloride. Tested I inhibited LPS-induced TNFα production in THP1 cells with IC50 = 0.17-1.77 μM.

IC A61K031-4155; A61K031-4709; C07D401-06; C07D405-06; C07D409-06
INCL 514314000
CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

IT Anti-inflammatory agents
Antiarthritics
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(production inhibitors; preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 165245-96-5, **p-38** MAP kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibitors; preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 249935-56-6P 249935-63-5P 249935-94-2P 249936-51-4P 249936-54-7P 249936-65-0P 249937-47-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 249935-54-4P 249935-55-5P 249935-57-7P 249935-58-8P 249935-59-9P

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331777-29-8P 331777-30-1P 331777-31-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 74-89-5, Methylamine, reactions 75-05-8, Acetonitrile, reactions 79-14-1, Glycolic acid, reactions 79-22-1, Methyl chloroformate 94-05-3, Ethyl ethoxymethylenecyanoacetate 100-63-0, Phenylhydrazine 106-96-7, Propargyl bromide 109-01-3, N-Methylpiperazine 109-70-6, 1-Bromo-3-chloropropane 109-89-7, Diethylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 111-42-2, Diethanolamine, reactions 111-95-5 124-40-3, Dimethylamine, reactions 141-43-5, 2-Aminoethanol, reactions 371-14-2, 4-Fluorophenylhydrazine 462-08-8, 3-Aminopyridine 504-29-0, 2-Aminopyridine 504-30-3, 3(2H)-Pyridazinone 540-51-2, 2-Bromoethanol 586-98-1, 2-Pyridinemethanol 614-16-4, Benzoylacetonitrile 615-00-9, 2,4-Dimethylphenylhydrazine 618-91-7, Methyl 3-iodobenzoate 626-55-1, 3-Bromopyridine 658-27-5, 3-Fluorophenylhydrazine 693-98-1, 2-Methylimidazole 822-36-6, 4-Methylimidazole 877-66-7, 4-Methylsulfonylphenylhydrazine 1711-09-7 1795-48-8, Isopropyl isocyanate 1820-80-0, 3-Aminopyrazole 1878-67-7, 3-Bromophenylacetic acid 2127-03-9, 2-Aldrithiol 2339-53-9, 3-Fluoro-6-methylphenylhydrazine 2386-58-5, Vinyl sulfonamide 2398-37-0, 3-Bromoanisole 2402-97-3, 3-Bromopyridine N-oxide 3445-11-2 3471-32-7, 4-Methoxyphenylhydrazine 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 5292-43-3, tert-Butyl bromoacetate 5382-16-1, 4-Hydroxypiperidine 7486-35-3, Vinyltributyltin 18312-46-4, 2-Methoxyphenylhydrazine 19275-55-9, 2-Ethylphenylhydrazine 19438-10-9, Methyl 3-hydroxybenzoate 23788-74-1 51304-65-5, 3-Chloro-4-methylphenylhydrazine 51934-41-9, Ethyl 4-iodobenzoate

58791-94-9 63693-65-2, 4-Isopropylphenylhydrazine 97674-02-7, Tributyl(1-ethoxyvinyl)tin 124252-41-1 131534-65-1, Pyridine-3-boronic acid, 1,3-propanediol cyclic ester 249937-03-9 249937-48-2 331777-17-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

IT 5799-76-8P 21667-64-1P 28229-69-8P 70591-86-5P 79601-27-7P 138907-68-3P 183158-31-8P 187949-90-2P 247206-80-0P 249936-98-9P 249936-99-0P 249937-00-6P 249937-02-8P 249937-05-1P 249937-06-2P 249937-07-3P 249937-08-4P 249937-09-5P 249937-10-8P 249937-11-9P 249937-12-0P 249937-13-1P 249937-16-4P 249937-18-6P 249937-21-1P 249937-22-2P 249937-25-5P 249937-44-8P 249937-45-9P 331777-15-2P 331777-16-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of aminoaroylarylpyrazoles as **p-38** MAP kinase inhibitors)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:331893 HCAPLUS
TITLE: Oxindolylidene derivatives as **p38** MAP kinase inhibitors.
AUTHOR(S): Cheng, Soan; Comer, Daniel, D.; Freire-Moar, Jose; **Goldstein, David, M.**; Myers, Peter, L.; Saunders, John; Sjogren, Eric, B.; Teig, Steve; Warren, Stephen; Whiteley, Phyllis, E.
CORPORATE SOURCE: Department of Medicinal Chemistry, CombiChem, Inc, San Diego, CA, 92121, USA
SOURCE: Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-282. American Chemical Society: Washington, D. C.
CODEN: 69CLAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Abstract: Several series of oxindolylidene derivs. were prepared for evaluation as p38 MAP kinase inhibitors. Base-catalyzed condensations of oxindoles with carbonyl compds. led to the formation of oxindolylidene derivs. The introduction of the benzoyl group at the 6-position of oxindoles is effective in obtaining potent analogs. Various arylidene and heteroarylidene groups at the C-3 position were evaluated. This work has resulted in several novel potent structures as p38 MAP kinase inhibitors. The most potent analog of the oxindole series is CC-8866, with an IC50 of 0.14 μM.

L47 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:282215 HCAPLUS
DOCUMENT NUMBER: 130:325138
TITLE: Preparation of pyrrolopyridines, furopyridines, and related compounds as **p-38** MAP kinase inhibitors.
INVENTOR(S): Cheng, Soan; **Goldstein, David Michael**; Martin, Teresa Alejandra Trejo; Sjogren, Eric Brian
PATENT ASSIGNEE(S): F.Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9920624	A1	19990429	WO 1998-EP6472	19981013
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2306870	AA	19990429	CA 1998-2306870	19981013
AU 9897499	A1	19990510	AU 1998-97499	19981013
AU 745579	B2	20020321		
TR 200001079	T2	20000721	TR 2000-200001079	19981013
BR 9812944	A	20000808	BR 1998-12944	19981013
EP 1025102	A1	20000809	EP 1998-951516	19981013
EP 1025102	B1	20040519		
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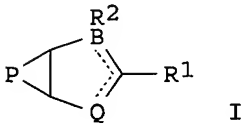
JP 2001520227	T2	20011030	JP 2000-516966	19981013
JP 3579350	B2	20041020		
RU 2219178	C2	20031220	RU 2000-110738	19981013
AT 267200	E	20040615	AT 1998-951516	19981013
ES 2221213	T3	20041216	ES 1998-951516	19981013
US 6316464	B1	20011113	US 1998-174299	19981016
ZA 9809529	A	19990420	ZA 1998-9529	19981019
TW 224596	B1	20041201	TW 1998-87117244	19981019
HR 2000000209	A1	20010430	HR 2000-209	20000412
NO 2000001940	A	20000413	NO 2000-1940	20000413
NO 316734	B1	20040419		
MX 200003810	A	20001113	MX 2000-3810	20000418
US 2001044538	A1	20011122	US 2001-839712	20010419
US 6479507	B2	20021112		
US 2002013354	A1	20020131	US 2001-839710	20010419
US 6630485	B2	20031007		
US 2003139462	A1	20030724	US 2002-245906	20020917

PRIORITY APPLN. INFO.:	US 1997-62548P	P	19971020
	US 1998-75515P	P	19980220
	US 1998-96916P	P	19980818
	WO 1998-EP6472	W	19981013
	US 1998-174299	A3	19981016
	US 2001-839712	A1	20010419

OTHER SOURCE(S): MARPAT 130:325138
GI



I

AB Title compds. [I; R1 = heteroaryl; when the dotted line is a double bond between Q and CR1, then B = N, R2 = aryl, and Q = CR; R = H, alkyl,

haloalkyl, cycloalkyl, NO2, cyano, amino, acylamino, etc.; when the dotted line = double bond between B and CR1, then B = C; R2 = aryl, heteroaryl; Q = imino, O, S; P = atoms to form (substituted) pyrido, pyridazino, pyrimidino, pyrazino rings], were prepared Thus, Me isonicotinate and 4-fluorophenylacetonitrile in EtOH were added to a solution prepared from EtOH and Na metal followed by 3 h reflux to give 2-(4-fluorophenyl)-1-(pyridin-4-yl)ethanone. The latter was azeotroped with 3-amino-2-chloropyridine and p-TsOH in PhMe to give (2-chloropyridin-3-yl)-[2-(4-fluorophenyl)-1-(pyridin-4-yl)vinyl]amine. This was heated with DABCO and (Ph3P)2PdCl2 in DMF to give 3-(4-fluorophenyl)-2-(pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine. Tested I inhibited p-38 kinase with IC50 = 68-246 nM.

IC ICM C07D471-04
ICS A61K031-435; A61K031-495; C07D491-048; C07D487-04; C07D495-04; C07D213-74; C07D213-75; C07D213-26; C07D213-70; C07D237-20; C07D241-18; C07D471-04; C07D221-00; C07D209-00; C07D491-048; C07D307-00; C07D221-00; C07D487-04; C07D241-00

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT Anti-inflammatory agents
(preparation of pyrrolopyridines, furopyridines, and related compds. as **p-38** MAP kinase inhibitors)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(production inhibitors; preparation of pyrrolopyridines, furopyridines, and related compds. as **p-38** MAP kinase inhibitors)

IT 165245-96-5, **p-38** MAP kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibitors; preparation of pyrrolopyridines, furopyridines, and related compds. as **p-38** MAP kinase inhibitors)

IT 223740-58-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pyrrolopyridines, furopyridines, and related compds. as **p-38** MAP kinase inhibitors)

IT 223738-89-4P 223738-90-7P 223738-91-8P 223738-92-9P 223738-93-0P
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223742-41-4P 223742-45-8P 223742-50-5P 223742-52-7P 223742-56-1P
223742-60-7P 223742-64-1P 223742-68-5P 223743-45-1P 223743-47-3P
223743-48-4P 223743-49-5P 223743-52-0P 223743-53-1P 223743-54-2P
223743-56-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolopyridines, furopyridines, and related compds. as **p-38** MAP kinase inhibitors)

IT 105-36-2, Ethyl bromoacetate 109-70-6, 1-Chloro-3-bromopropane 156-87-6, 3-Amino-1-propanol 352-11-4, 4-Fluorobenzyl chloride 459-22-3, 4-Fluorophenylacetonitrile 822-36-6, 4-Methylimidazole 874-24-8, 3-Hydroxypicolinic acid 1120-87-2, 4-Bromopyridine 1122-54-9, 4-Acetylpyridine 2008-75-5, 1-(2-Chloroethyl)piperidine hydrochloride 2459-09-8, Methyl isonicotinate 3647-69-6 5470-18-8, 2-Chloro-3-nitropyridine 6298-19-7, 3-Amino-2-chloropyridine 6313-54-8, 2-Chloropyridine-4-carboxylic acid 14254-57-0, Isonicotinoyl chloride 14508-49-7, Chloropyrazine 17282-00-7, 2-Amino-3-bromo-5-methylpyridine 58481-11-1, Methyl 2-chloropyridine-4-carboxylate 70298-89-4 116332-54-8 130387-74-5, 4-Fluorophenylmagnesium chloride 223743-44-0 223743-46-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrrolopyridines, furopyridines, and related compds. as **p-38** MAP kinase inhibitors)

IT 54608-52-5P 73406-50-5P, Ethyl 3-hydroxypicolinate 115858-98-5P 223742-77-6P 223742-81-2P 223742-86-7P 223742-89-0P 223742-93-6P 223742-96-9P 223743-01-9P 223743-04-2P 223743-07-5P 223743-09-7P 223743-14-4P 223743-15-5P 223743-18-8P 223743-21-3P 223743-23-5P 223743-26-8P 223743-28-0P 223743-30-4P 223743-33-7P 223743-36-0P 223743-37-1P 223743-38-2P 223743-39-3P 223743-42-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrrolopyridines, furopyridines, and related compds. as **p-38** MAP kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 24 OF 24 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-656837 [67] WPIX
DOC. NO. CPI: C2005-198580
TITLE: New heteroaryl-fused pyrazolo derivatives are p38 kinase inhibitors useful to treat e.g. arthritis, Crohn's disease, Alzheimer's disease, influenza, multiple sclerosis, cancer, diabetes and psoriasis.
DERWENT CLASS: B02
INVENTOR(S): ARORA, N; BILLEDEAU, R J; **DEWDNEY, N J**; GABRIEL, T; **GOLDSTEIN, D M**; MCCALEB, K L; SOTH, M; TREJO-MARTIN, T A
PATENT ASSIGNEE(S): (ROCH-N) ROCHE PALO ALTO LLC; (HOFF) HOFFMANN LA ROCHE & CO AG F; (MCCA-I) MCCALEB K L
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2005203091	A1	20050915	(200567)*		64
WO 2005085248	A1	20050915	(200567)	EN	

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005203091	A1 Provisional	US 2004-548642P	20040227
		US 2005-65890	20050225
WO 2005085248	A1	WO 2005-EP1815	20050222

PRIORITY APPLN. INFO: US 2004-548642P 20040227; US 2005-65890 20050225

AN 2005-656837 [67] WPIX

AB US2005203091 A UPAB: 20051019

NOVELTY - Heteroaryl-fused pyrazolo derivatives (I) and their salts, solvates or prodrugs are new.

DETAILED DESCRIPTION - Heteroaryl-fused pyrazolo derivatives of formula (I) and their salts, solvates or prodrugs are new.

R1 = (hetero)aryl (optionally substituted) or cycloalkyl;

R2 = (hetero)aryl (optionally substituted), cycloalkyl, branched alkyl, iodo or heterocyclyl;

R3, R6, R9 = H or alkyl;

X, Y, Z = N or CR;

R4 = H, alkyl, halo, amino, alkoxy, hydroxy, cyano, heteroalkyl, heterocyclyl, hydroxycycloalkyl or -C(=O)-R5;

R5, R10 = hydroxy, alkoxy, amino, (hetero)alkyl, aralkyl, (hetero)aryl or heterocyclyl;

A = O, CH2, S(O)n, C(=O), CH2(OR6), NR7 or CH2NR7; either

R7 = H or alkyl; or

R1+R7 = heterocyclyl;

n, j = 0-2;

k = 0 or 1;

B = O, NR8, S(O)j, CH(OR9), CH=CH or C(=O);

R8 = H, alkyl or -C(=O)-R10; and

R11 = alkyl.

Provided that when A is NR6, R1 is not 5-methanesulfonyl-2-methoxyphenyl; and one or two of X, Y, Z is N.

ACTIVITY - Antiarthritic; Antiinflammatory; Gastrointestinal-Gen.; Respiratory-Gen.; Neuroprotective; Nootropic; Virucide; Cytostatic; Antidiabetic; Dermatological; Immunosuppressive; Antipsoriatic; Vulnerary; Antiulcer; Ophthalmological; Antiangiogenic; Nephrotropic; Cardiovascular-Gen.; Gynecological; Analgesic; Antiasthmatic; Anti-HIV; Hepatotropic; Osteopathic; Antibacterial; Vasotropic; Antiarteriosclerotic; Thrombolytic.

MECHANISM OF ACTION - P38 kinase inhibitor.

The ability of (I) to inhibit p38 kinase was tested using biological assays. The results showed that the median inhibitory concentration of

3-(2-chloro-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo(3,4-d)pyrimidine was 0.01 mu m).

USE - (I) are useful for the treatment of p38 mediated disorders (arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome or chronic obstructive pulmonary disease) (claimed). (I) are useful for the treatment of Alzheimer's disease, influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythrematosis, skin-related conditions such as psoriasis, eczema, burns, dermatitis, keloid formation and scar tissue formation. (I) are also useful for the treatment of gastrointestinal conditions such as inflammatory bowel disease, gastritis and ulcerative colitis; ophthalmic diseases; angiogenesis; metastasis; diabetic retinopathy; non-malignant conditions such as infantile hemangiomas; diabetic nephropathy and cardiomyopathy; disorders of the female reproductive system such as endometriosis; pain; hepatitis C virus; severe asthma; AIDS; pneumonia and herpes virus; bone resorption diseases, endotoxic shock, reperfusion injury, autoimmune disease such as graft vs. host reaction and allograft rejections; cardiovascular diseases such as atherosclerosis, thrombosis, congestive heart failure, cardiac reperfusion injury, renal reperfusion injury, liver disease or nephritis.
Dwg.0/0

```
=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 14:44:59 ON 19 JUL 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE SEARCH


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FILE COVERS 1907 - 19 Jul 2006  VOL 145 ISS 4
FILE LAST UPDATED: 18 Jul 2006  (20060718/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d stat que L6
L3               STR
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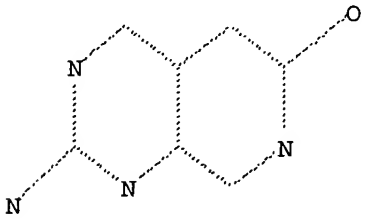


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Structure attributes must be viewed using STN Express query preparation.
L5             7 SEA FILE=REGISTRY SSS FUL L3
L6             2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5

=> s L6 not L45
L49            1 L6 NOT L45
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→ printed with author search

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FILE LAST UPDATED:          14 JUL 2006      <20060714/UP>
MOST RECENT DERWENT UPDATE:     200645        <200645/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <
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>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
    INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
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L29             1 SEA FILE=WPIX ABB=ON  PLU=ON  (979788-1-0-0/DCRE OR 979789-0-0-
                  0/DCRE OR 979790-0-0-0/DCRE OR 979791-0-0-0/DCRE OR 979792-0-0-
                  0/DCRE)
L30             1 SEA FILE=WPIX ABB=ON  PLU=ON  L28 OR L29


=> s L30 not L46
L50             0 L30 NOT L46
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=> file marpat
FILE 'MARPAT' ENTERED AT 14:46:10 ON 19 JUL 2006
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FILE CONTENT: 1961-PRESENT VOL 145 ISS 1 (20060714/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US   2006118302 08 JUN 2006
DE 102004053653 04 MAY 2006
EP      1653548 03 MAY 2006
JP   2006112980 27 APR 2006
WO   2006053912 26 MAY 2006
GB      2419594 03 MAY 2006
FR      2877004 28 APR 2006
RU      2275374 27 APR 2006
CA      2518664 10 MAR 2006

Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.


=> d stat que L21
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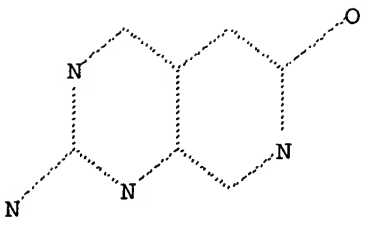

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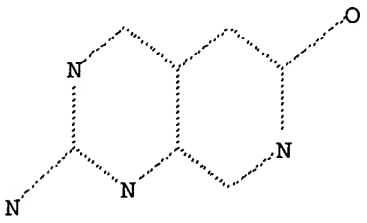

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SEARCH TIME: 00.00.01

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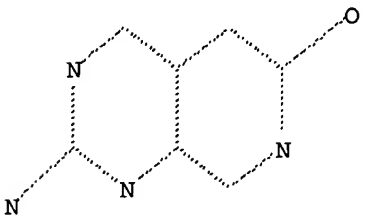

Structure attributes must be viewed using STN Express query preparation.
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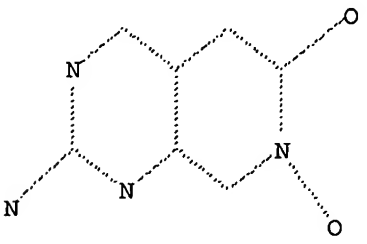
L22 STR



Structure attributes must be viewed using STN Express query preparation.
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100.0% PROCESSED 18 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

=> s (L21 or L24) not L39
L51 13 (L21 OR L24) NOT (L39) → printed with author search

=> file beilstein
FILE 'BEILSTEIN' ENTERED AT 14:47:23 ON 19 JUL 2006
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FILE LAST UPDATED ON JUNE 16, 2006

FILE COVERS 1771 TO 2006.
*** FILE CONTAINS 9,606,495 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in
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Reaction data for BEILSTEIN compounds may be displayed
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for a chemical name, a compounds with available reaction
information by combining with PRE/FA, REA/FA or more generally
with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
between a BEILSTEIN compound and belonging reactions. For mo
detailed reaction searches BRNs can be searched as reaction
partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

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**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE   *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE          *
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NEW
*** PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.**
*** NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.**

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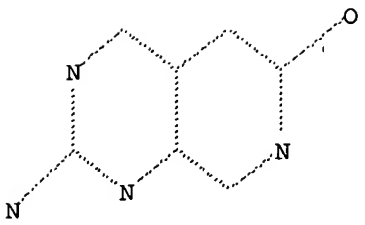
L3 STR



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SEARCH TIME: 00.00.02

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L8 HAS NO ANSWERS
DUPLICATE IS NOT AVAILABLE IN 'BEILSTEIN'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'HCAPLUS' ENTERED AT 14:47:53 ON 19 JUL 2006
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PROCESSING COMPLETED FOR L49
PROCESSING COMPLETED FOR L50
PROCESSING COMPLETED FOR L51
PROCESSING COMPLETED FOR L8
L52 14 DUP REM L49 L50 L51 L8 (0 DUPLICATES REMOVED)
ANSWER '1' FROM FILE HCAPLUS
ANSWERS '2-14' FROM FILE MARPAT

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L52 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:857326 HCAPLUS
DOCUMENT NUMBER: 141:309639
TITLE: Dipeptidyl peptidase inhibitors
INVENTOR(S): Feng, Jun; Gwaltney, Stephen L.; Kaldor, Stephen W.; Stafford, Jeffrey A.; Wallace, Michael B.; Zhang, Zhiyuan
PATENT ASSIGNEE(S): Syrrx, Inc., USA
SOURCE: PCT Int. Appl., 244 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004087053	A2	20041014	WO 2004-US9217	20040324
WO 2004087053	C2	20041111		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2518465	AA	20041014	CA 2004-2518465	20040324
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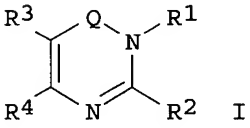
US 2004242566	A1	20041202	US 2004-809638	20040324
US 2004259870	A1	20041223	US 2004-809637	20040324
US 2005004117	A1	20050106	US 2004-809635	20040324
EP 1608317	A2	20051228	EP 2004-758366	20040324
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.: US 2003-457785P P 20030325
WO 2004-US9217 W 20040324

OTHER SOURCE(S): MARPAT 141:309639

GI



I

AB Dipeptidyl peptidase IV inhibitors I [Q = CO, SO, SO2, C:NR5; R1 = ZR6; Z = moiety providing 1-6 atom separation between R6 and ring; R2 = (substituted)3-7-membered ring; R3,R4 = taken together form a (substituted)5-6-membered ring; R5 = H, (substituted)alkyl, cycloalkyl, etc.; R6 = (substituted)C3-7-cycloalkyl or aryl] are disclosed. Thus, 2-[2-(3-aminopiperidin-1-yl)-6,7-dimethoxy-4-oxo-4H-quinazolin-3-ylmethyl]benzonitrile (I; R1 = 2-cyanophenylmethyl; R2 = 3-aminopiperidin-1-yl; R3,R4 = dimethoxyphenyl) was synthesized. This compound exhibited enhanced stability in rat liver microsomes.

IC ICM A61K

CC 7-3 (Enzymes)

IT 22126-97-2P 80096-35-1P 769157-54-2P 769157-55-3P 769157-56-4P
769157-57-5P 769157-58-6P 769157-59-7P 769157-60-0P 769157-61-1P
769157-62-2P 769157-63-3P 769157-65-5P **769157-67-7P**
769157-69-9P 769157-71-3P 769157-73-5P 769157-75-7P 769157-77-9P
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769158-00-1P 769158-01-2P 769158-02-3P 769158-03-4P 769158-04-5P
769158-05-6P 769158-06-7P 769158-14-7P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(dipeptidyl peptidase inhibitors)

IT **769157-67-7P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(dipeptidyl peptidase inhibitors)

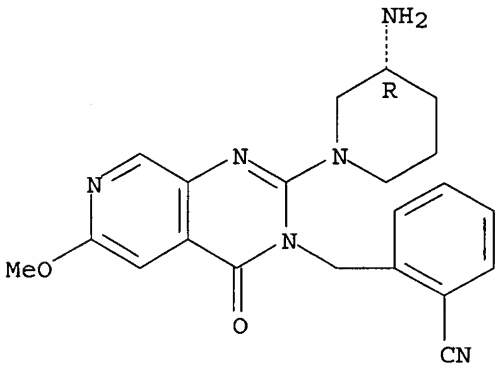
RN 769157-67-7 HCAPLUS

CN Benzonitrile, 2-[[2-[(3R)-3-amino-1-piperidinyl]-6-methoxy-4-oxopyrido[3,4-d]pyrimidin-3(4H)-yl]methyl]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 769157-66-6
CMF C21 H22 N6 O2

Absolute stereochemistry.



CM 2

CRN 76-05-1
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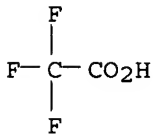


L52 ANSWER 2 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 142:455888 MARPAT
TITLE: Halogenated coordination compounds preparation and use thereof
INVENTOR(S): Schwaiger, Jochen; Bach, Ingrid; Stoessel, Philipp
PATENT ASSIGNEE(S): Covion Organic Semiconductors G.m.b.H., Germany
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042545	A2	20050512	WO 2004-EP11891	20041021
WO 2005042545	A3	20060105		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

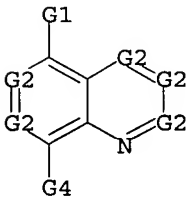
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10351556	A1	20050602	DE 2003-10351556	20031103

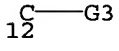
PRIORITY APPLN. INFO.: DE 2003-10351556 20031103
OTHER SOURCE(S): CASREACT 142:455888

AB The invention relates to novel halogenated coordination compds. containing azanaphthalenols/thiols/selenols, of application as functional materials in differing applications within the widest sense of the electronic industry and which comprise organically-bonded halides as reactive groups. The invention further relates to a method for regioselective preparation of said compds. For example, AlL2 (HL = 8-hydroxyquinoline) was brominated with N-bromosuccinimide to give AlL13 (HL1 = 5-bromo-8-hydroxyquinoline) in 99 % yield.

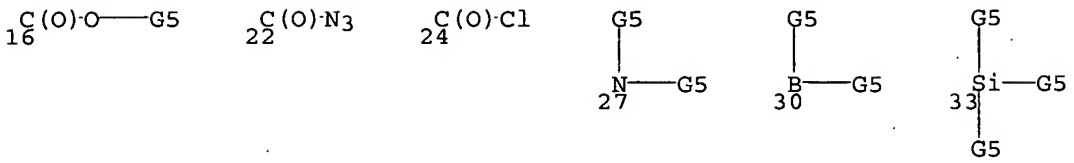
MSTR 1

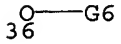


G1 = Cl / F / Br / I / H
G2 = **N** / **12**

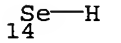


G3 = H / F / Cl / Br / I / CN / CHO / 16 / 22 / 24 / **NO2** / 27 / 30 / 33 / carbon chain <containing 1 or more C> (opt. substd.) / **36**





G4 = OH / SH / 14 / aryl <containing up to 40 C>
(opt. substd.) / heteroaryl <containing up to 40 atoms,
zero or more O, zero or more S,
zero or more N (no other heteroatoms)> (opt. substd.)



G5 = H / R
G6 = carbon chain <containing 1 or more C>
(opt. substd.) / aryl <containing up to 40 C>
(opt. substd.) / heteroaryl <containing up to 40 atoms,
zero or more O, zero or more S,
zero or more N (no other heteroatoms)> (opt. substd.)
G10 = R <"metal"> / (Specifically claimed: Al / Be / B /
Ca / Ga / In / Ir / Li / Mg / Zn)
Patent location: claim 1
Note: as complexes with G10
Note: additional ligands and ring formation also claimed
Note: also incorporates claim 13, structure IV

L52 ANSWER 3 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 142:463438 MARPAT
TITLE: Preparation of phenylamine substituted bicyclic heterocyclic compounds useful as kinase inhibitors
INVENTOR(S): Das, Jagabandhu; Hynes, John; Leftheris, Katerina; Lin, Shuqun; Wrobleski, Stephen T.; Wu, Hong
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042537	A1	20050512	WO 2004-US35116	20041022

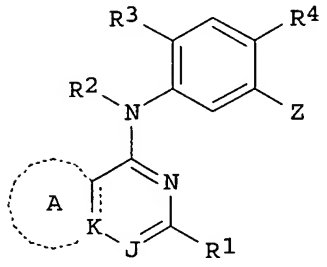
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005143398 A1 20050630 US 2004-970420 20041021

PRIORITY APPLN. INFO.: US 2003-513285P 20031022

GI



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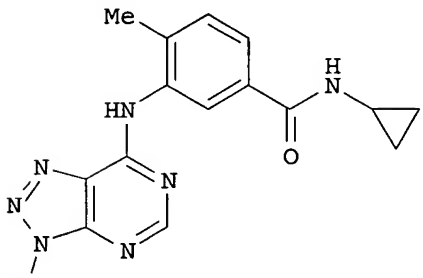
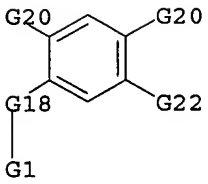


II

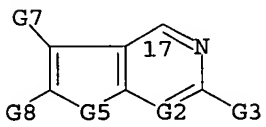
AB Title compds. I [J = N or CR5; R1 and R5 independently = H, OH, halo, CN, etc.; R2 = H or alkyl; R3 and R4 independently = H, (un)substituted-alkyl, OH, MeO, halo, etc.; K = N or C; Z = NHR6, CONR6R7, NR6CO2R7, etc.; R6 = H or (un)substituted alkyl; R7 = H, OH, alkoxy, etc.; Ring A = fused heterocycle or carbocycle], and their pharmaceutically acceptable salts, prodrugs, and solvates thereof, are prepared and disclosed as kinase inhibitors. Thus, e.g., II was prepared by reaction of 4-chloro-1-phenyl-1,2,3,5,7-azaindene with 3-amino-4-methyl-N-cyclopropylbenzamide. I have shown activity as inhibitors of p38α/β enzymes and TNF-α (no data).

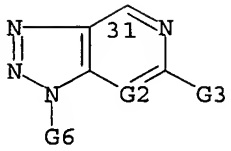
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

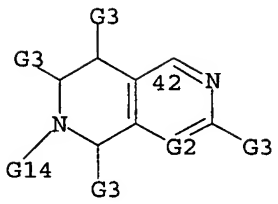
MSTR 1

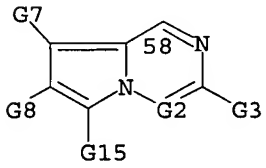


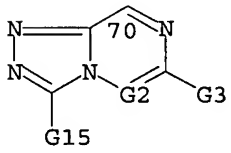
G1 = 17 / 31 / **42** / 58 / 70 / 82

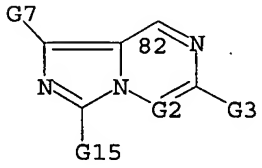










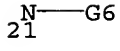


G2 = **N** / 18

G3 = H / alkyl <containing 1-12 C> (opt. substd.) / **OH** / alkoxy <containing 1-12 C> / F / Cl / Br / I / CN / **NH2** / alkylamino <containing 1-12 C> (opt. substd.) / dialkylamino <each alkyl containing 1-12 C> (opt. substd.) / alkoxy <containing 1-12 C> (substd. by 1 or more G4) / carbocycle <0 or more double bonds> (opt. substd.) / aryl (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.)

G4 = F / Cl / Br / I

G5 = 21 / S

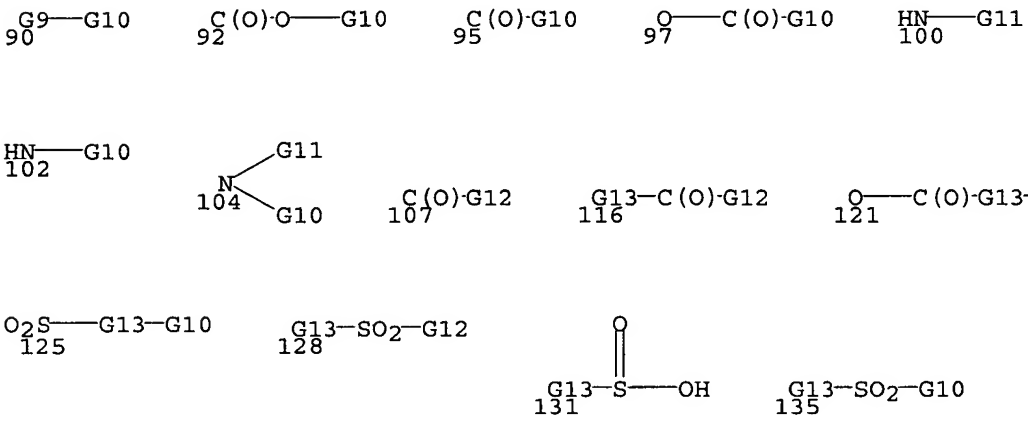


G6 = alkyl <containing 1-12 C> (opt. substd.) / aryl (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / (Specifically claimed: Ph (opt. substd.))

G7 = H / Me / CF3 / OMe / F / Cl / Br / I / CN / NH2 / NHMe

G8 = H / carbon chain <containing 1-12 C>

(opt. substd.) / aryl (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.) / F / Cl / Br / I / CN / NO2 / OH / SH / 90 / CO2H / 92 / CHO / 95 / OCHO / 97 / NH2 / 100 / 102 / 104 / 107 / 116 / 121 / 125 / 128 / 131 / 135 / 138 / 140 / (Specifically claimed: 234)

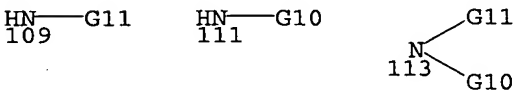


G9 = O / S / S(O) / SO2

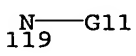
G10 = carbon chain <containing 1-12 C> (opt. substd.) / aryl (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.)

G11 = alkyl <containing 1-12 C> (opt. substd.) / aryl (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.)

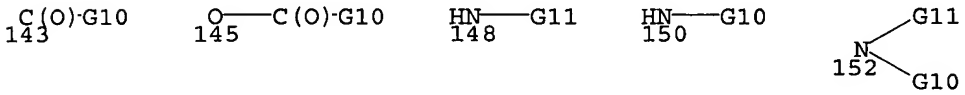
G12 = NH2 / 109 / 111 / 113

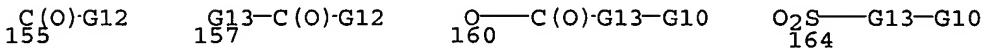


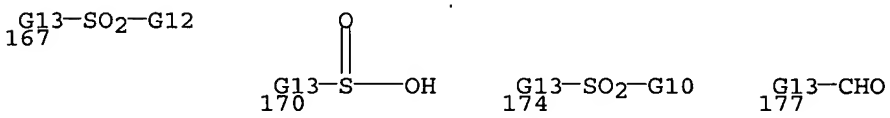
G13 = NH / 119

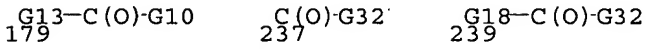


G14 = H / NO2 / CHO / 143 / OCHO / 145 / NH2 / 148 / 150 / 152 / 155 / 157 / 160 / 164 / 167 / 170 / 174 / 177 / 179 / carbon chain <containing 1-12 C> (opt. substd.) / aryl (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.) / (Specifically claimed: 237 / 239)

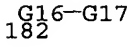




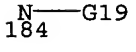




G15 = H / alkyl <containing 1-12 C> (opt. substd.) / F / Cl / Br / I / CN / aryl (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / 182 / (Specifically claimed: Ph)

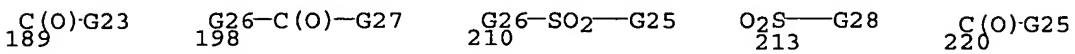


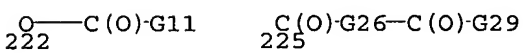
G16 = S / SO2
G17 = alkyl <containing 1-12 C> (opt. substd.)
G18 = NH / 184



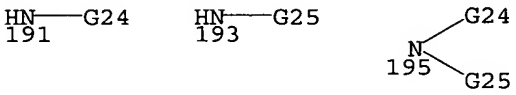
G19 = alkyl <containing 1-4 C>
G20 = H / alkyl <containing 1-4 C> (opt. substd. by (1-2) G21) / OH / OMe / F / Cl / Br / I / CN / NH2 / alkylamino <containing 1-4 C> / dialkylamino <each alkyl containing 1-4 C> / CF3 / OCF3 / (Specifically claimed: Me)
G21 = OH / OMe / F / Cl / Br / I / CN / NH2 / alkylamino <containing 1-4 C> / dialkylamino <each alkyl containing 1-4 C> / CF3 / OCF3

G22 = NH2 / alkylamino <containing 1-12 C> (opt. substd.) / 189 / 198 / 210 / 213 / CHO / 220 / OCHO / 222 / 225 / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.)

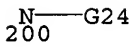




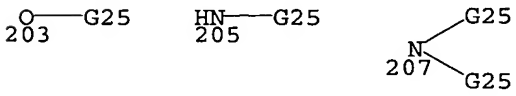
G23 = NH2 / 191 / 193 / 195



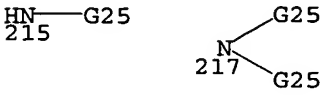
G24 = alkyl <containing 1-12 C> (opt. substd.)
G25 = alkyl <containing 1-12 C> (opt. substd.) / alkenyl <containing 2-20 C, up to 4 double bonds> (opt. substd.) / OH / alkoxy <containing 1-12 C> / aryl (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / (Specifically claimed: cyclopropyl / pyrazolyl / oxazolyl / isoxazolyl / Ph / pyridyl)
G26 = NH / 200



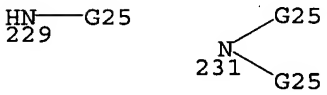
G27 = OH / 203 / H / alkyl <containing 1-12 C> (opt. substd.) / alkenyl <containing 2-20 C, up to 4 double bonds> (opt. substd.) / OH / alkoxy <containing 1-12 C> / aryl (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / NH2 / 205 / 207



G28 = NH2 / 215 / 217



G29 = H / alkyl <containing 1-12 C> (opt. substd.) / alkenyl <containing 2-20 C, up to 4 double bonds> (opt. substd.) / OH / alkoxy <containing 1-12 C> / aryl (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / heterocycle <containing zero or more N, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / NH2 / 229 / 231

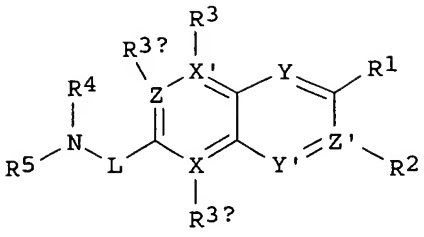


G30 = H / alkyl <containing 1-6 C> / alkoxy <containing 1-6 C> / carbocycle <containing 3-7 C> / morpholino / alkyl <containing 1-4 C> (substd. by 1 or more G31) / (Specifically claimed: CH2Ph)
G31 = Ph / pyridyl
G32 = alkyl <containing 1-6 C> (opt. substd. by 1 or more G33) / imidazolyl / pyrazolyl / pyridyl / Ph / morpholino
G33 = Ph / morpholino
Patent location: claim 1
Note: substitution is restricted
Note: additional substitution also claimed
Note: and pharmaceutically acceptable salts, prodrugs, and solvates
Stereochemistry: and enantiomers or diastereomers

L52 ANSWER 4 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 144:36332 MARPAT
TITLE: Preparation of tri-and bi-cyclic heteroaryl histamine-3 receptor ligands
INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang, Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser, Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005272736	A1	20051208	US 2005-123324	20050506
PRIORITY APPLN. INFO.:			US 2004-570397P	20040512

GI



I

AB Title compds. I [Y and Y' independently = CH, CF, and N; X, X', Z and W independently = C or N; one of R1 and R2 is selected from L2R6 with the other of R1 and R2 = H, alkyl, alkoxy, etc.; L2 = O, CO, S, NH, etc.; R6 = bicyclic or tricyclic ring, each containing at least two heteroatoms; R3 = H, alkyl, alkoxy, halo, etc., or R3 is absent when X' = N; R3a = H, Me, alkoxy, halo, etc., or R3a is absent when Z = N; R3b = H, OH, alkyl, alkoxy, etc., or R3b is absent when X = N; R4 and R5 independently = alkyl, haloalkyl, hydroxyalkyl, etc.; or R4 and R5 taken together to form heterocyclic ring], and their pharmaceutically acceptable salts, are prepared and disclosed as useful in treating conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Also disclosed are pharmaceutical compns. comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing I. Thus, e.g., 6-[2-((2R)-2-methylpyrrolidin-1-yl)ethyl]-2-(4H-thieno[3,2-b]pyrrol-5-yl)quinoline was prepared via a multistep synthesis from (S)-Toluene-4-sulfonic acid 5-oxopyrrolidin-2-ylmethyl ester. In histamine-3 receptor binding studies, I demonstrated binding affinities from 810 nM to 0.02 nM.

MSTR 1A

G9—G8—G7—G6—G14
40 28 27 13 15

G1 = **N** / **11**

C—G2
11

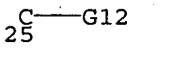
G2 = H / F
G3 = N / **21**

C—G20
21

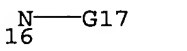
G4 = **N** / 23

C—G21
23

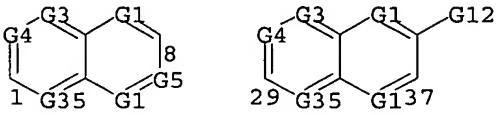
G5 = **N** / 25



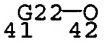
G6 = O / C(O) / S / alkylene <containing 1-4 C, unbranched> (opt. substd. by 1 or more G15) / G16 / **NH** / 16 / 18-27 19-15



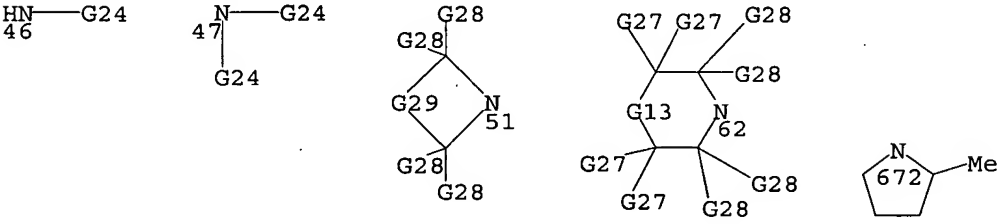
G7 = **1-28 8-13** / 29-28 37-13



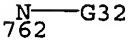
G8 = alkylene <containing 1-6 C> (opt. substd. by 1 or more G10) / G11 / **41-40 42-27**



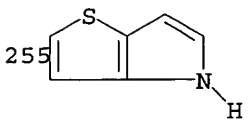
G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms, 1-3 heteroatoms, 1 or more N, zero or more O, zero or more S (no other heteroatoms), attached through 1 or more N, non-aromatic, 0 or more double bonds, mono- or bicyclic> (opt. substd. by 1 or more G26) / 51 / 62 / (Specifically claimed: 672)

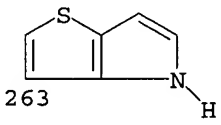


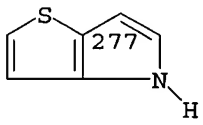
G10 = alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / aryl (opt. substd.) / cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN / alkylthio <containing 1-10 C>
G13 = O / S / 762 / bond

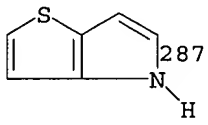


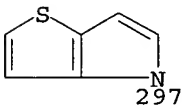
G14 = heterocycle <containing 2 or more heteroatoms, zero or more N, zero or more O, zero or more S, 2-3 rings> / (Specifically claimed: 255 / 263 / 277 / 287 / 297 / 309 / 319 / 330 / 344 / 351 / 364 / 374 / 382 / 390 / 401 / 417 / 429 / 437 / 446 / 458 / 461 / 473 / 481 / 489 / 500 / 514 / benzothiazolyl / benzotriazolyl / 525 / 532 / 539 / 555 / 561 / 573 / 579 / 586 / 597 / 604 / 607 / 619 / 635 / 646 / 655 / 664 / quinoxalinyl / 680 / 697 / 711 / 714 / 725 / 736 / 753)

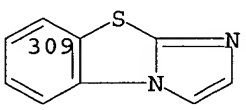


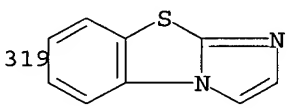


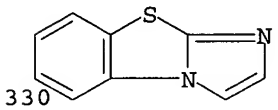


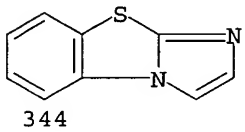


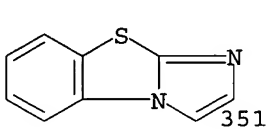


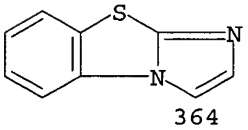


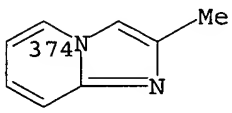


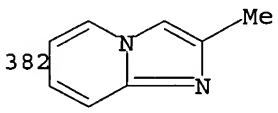


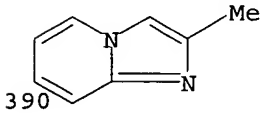


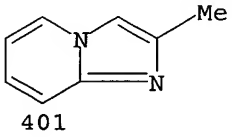


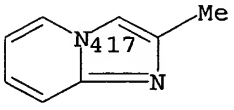


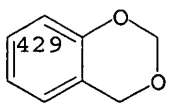


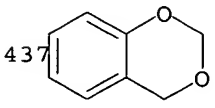


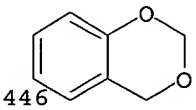


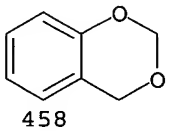


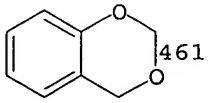


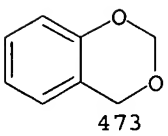








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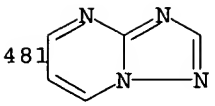
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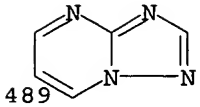
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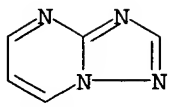
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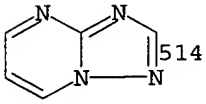
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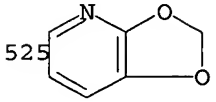
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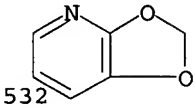
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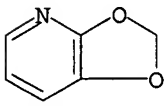
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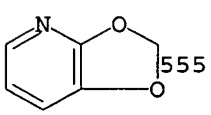
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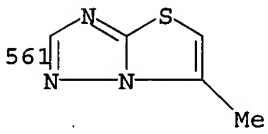
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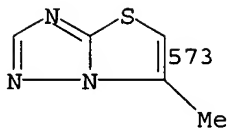
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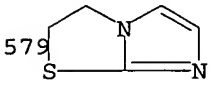
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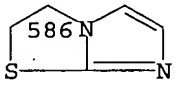
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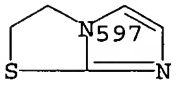
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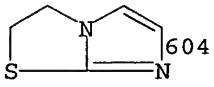
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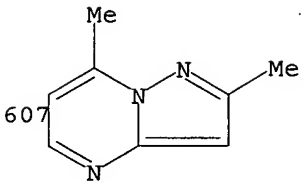
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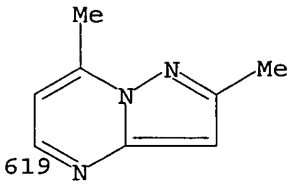
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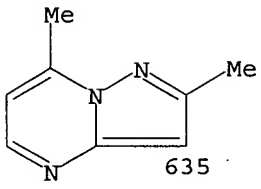
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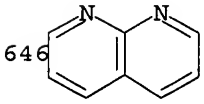
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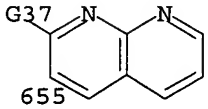
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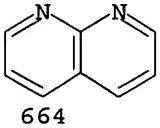
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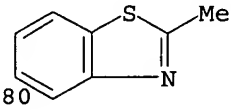
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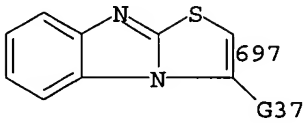
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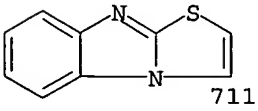
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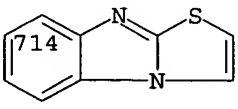
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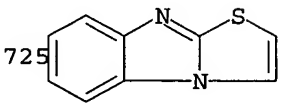
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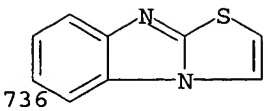
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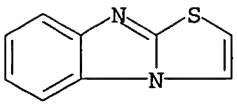

753

G15 = OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G16 = (1-4) CH2
G17 = alkyl <containing 1-10 C>
G19 = alkylene <containing 1-4 C, unbranched>
(opt. substd. by 1 or more G15) / G16
G20 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
I / CN
G22 = alkylene <containing 2-6 C>
(opt. substd. by 1 or more G10) / G23
G23 = (2-6) CH2
G24 = alkyl <containing 1-10 C>
(opt. substd. by 1 or more G25) /
cycloalkyl <containing 3-8 C>
G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F /
alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C>
/ CONH2 / CHO / alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
G27 = H / OH / alkyl <containing 1-10 C>
(opt. substd. by OH) / F
G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F)
G29 = (1-5) 57

G30—C(57)—G30

G30 = H / OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F
G32 = H / alkyl <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / CONH2 / CHO /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
G35 = N / **252**

C(252)—G36

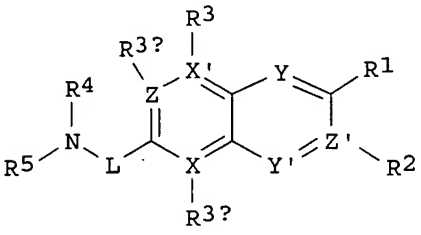
G36 = H / alkyl <containing 1-10 C> /

alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN / alkylthio <containing 1-10 C>
G37 = H / Me
Patent location: claim 1
Note: substitution is restricted
Note: or pharmaceutically acceptable salts, esters, amides, or prodrugs

L52 ANSWER 5 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 144:36264 MARPAT
TITLE: Preparation of bicyclic amines bearing heterocyclic substituents as H3 receptor ligands
INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang, Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser, Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 42 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005272728	A1	20051208	US 2005-123620	20050506
PRIORITY APPLN. INFO.:			US 2004-570186P	20040512

GI

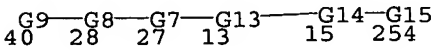


I

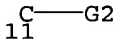
AB Title compds. I [Y, Y' = CH, CF, N; X, X', Z, Z' = C, N; R1, R2 = H, alkyl, alkoxy, aryl, cycloalkyl, etc.; R3 = absent when X' is N or H, alkyl, alkoxy, etc.; R3 = absent when X' is N or R3 = H, alkyl, alkoxy, halo, etc.; R3a = absent when Z is N or R3a = H, Me, alkoxy, halo, CN; R3b = absent when X is N or R3b = H, alkyl, alkoxy, halo, etc.; R4-5 = alkyl, haloalkyl, hydroxyalkyl, etc.; L = divalent alkyl, etc.] are prepared For instance, 6-[2-((2R)-2-methylpyrrolidin-1-yl)ethyl]-2-(4-methyl-2-thien-2-yl-1,3-thiazol-5-yl)quinoline is prepared in 7 steps from (S)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate, 1-(2-bromoethyl)-4-nitrobenzene, trimethylacetyl chloride, DMF and 1-(4-methyl-2-(thiophene-2-yl)thiazol-5-yl)ethanone. Representative compds. of the invention demonstrated binding affinities for the H3 receptor from about 810 nM to about 0.02 nM. I are useful for the treatment of conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Also disclosed are pharmaceutical compns.

comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing I.

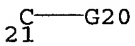
MSTR 1A



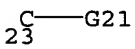
G1 = **N** / **11**



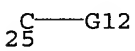
G2 = H / F
G3 = N / **21**



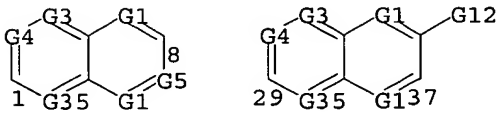
G4 = **N** / 23



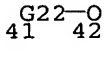
G5 = **N** / 25



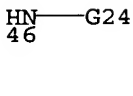
G7 = **1-28 8-13** / 29-28 37-13

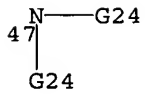


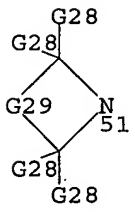
G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / **41-40 42-27**

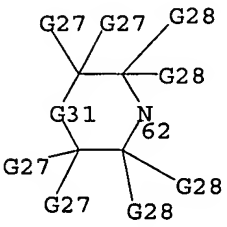


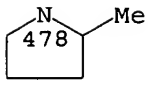
G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 478)



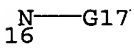


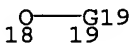




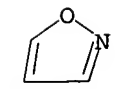


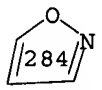
G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / aryl (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C> / (Specifically claimed: Me)
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd.) / **NH** / 16 / 18-27 19-15

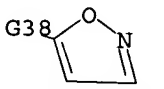


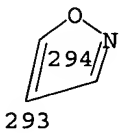


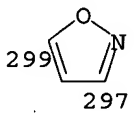
G14 = any ring <containing 5-8 atoms, zero or more N,
zero or more O, zero or more S> /
(Specifically claimed: phenylene / 277-13 278-254 /
282-13 284-254 / 288-13 287-254 / 293-13 294-254 /
299-13 297-254 / 304-13 303-254 / 310-13 309-254 /
316-13 314-254 / 322-13 318-254 / 327-13 328-254 /
333-13 332-254 / 339-13 336-254 / 342-13 346-254 /
348-13 351-254 / 354-13 356-254 / 361-13 363-254 /
366-13 365-254 / 371-13 369-254 / 378-13 376-254 /
383-13 380-254 / 388-13 384-254 / 392-13 393-254 /
397-13 400-254 / 402-13 401-254 / 409-13 411-254 /
414-13 417-254 / 421-13 419-254 / 426-13 427-254 /
432-13 429-254 / 437-13 436-254 / 438-13 439-254 /
443-13 447-254 / 448-13 451-254 / 454-13 453-254 /
459-13 462-254 / 464-13 466-254 / 468 / 473-13 475-254 /
heterocycle <containing 5 atoms, 3 N, 2 C, aromatic,
2 double bonds, 5-membered monocyclic ring> /
532-13 533-254 / 538-13 539-254)

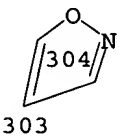


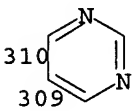


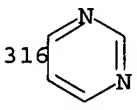


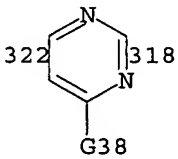


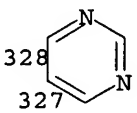


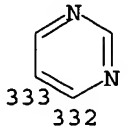


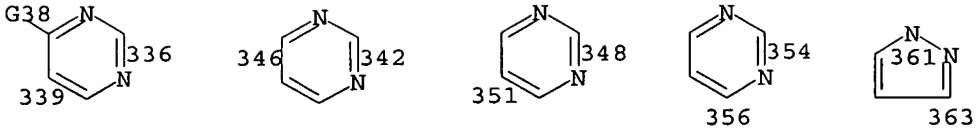


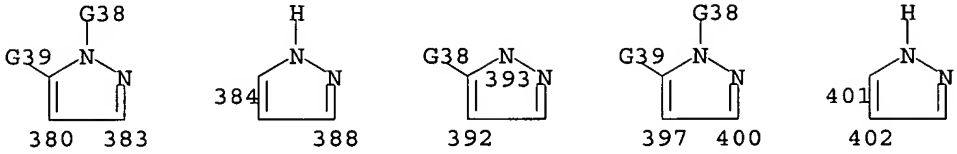


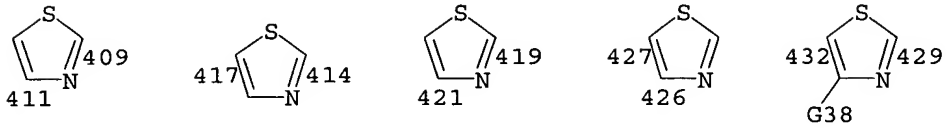


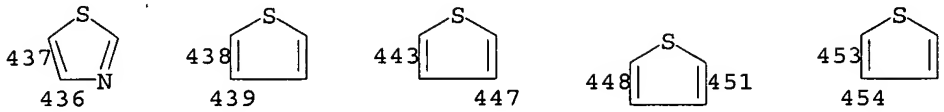


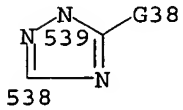










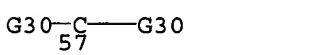


G15 = G37 / 255

G16—G37
255 256

G16 = R <"linking group"> / (Specifically claimed: 271-15 272-256 / 273-15 274-256)

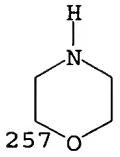
G17 = alkyl <containing 1-10 C>
G19 = alkylene <containing 1-4 C, unbranched> (opt. substd.)
G20 = H / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / F / Cl / Br / I / CN / alkylthio <containing 1-10 C>
G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br / I / CN
G22 = alkylene <containing 2-6 C> (opt. substd. by 1 or more G10) / G23
G23 = (2-6) CH2
G24 = alkyl <containing 1-10 C> (opt. substd. by 1 or more G25) / cycloalkyl <containing 3-8 C>
G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> / cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
G26 = H / alkyl <containing 1-10 C> (substd. by OH) / alkyl <containing 1-10 C> (substd. by 1 or more F) / OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> / dialkylamino <each alkyl containing 1-10 C> / F / alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C> / CONH2 / CHO / alkylaminocarbonyl <containing 1-10 C> / dialkylaminocarbonyl <each alkyl containing 1-10 C>
G27 = H / OH / alkyl <containing 1-10 C> (opt. substd. by OH) / F
G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) / alkyl <containing 1-10 C> (substd. by 1 or more F)
G29 = (1-5) 57

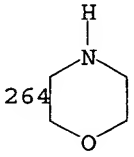


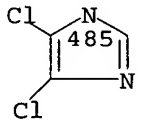
G30 = H / OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> / dialkylamino <each alkyl containing 1-10 C> / F
G31 = bond / O / S / 73

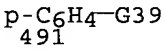
G32 = H / alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C> / CONH2 / CHO / alkylaminocarbonyl <containing 1-10 C> / dialkylaminocarbonyl <each alkyl containing 1-10 C>
G35 = N / **252**

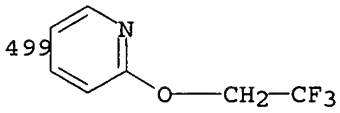
G36 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
alkylthio <containing 1-10 C>
G37 = any ring <containing 5-8 atoms, zero or more N,
zero or more O, zero or more S> /
(Specifically claimed: isoxazolyl / morpholino / 257 / 264 /
491 / pyridazinyl / pyridyl / pyrimidinyl / pyrazinyl /
pyrazolyl / thiadiazolyl / thiazolyl / thienyl / triazolyl /
cyclobutyl / pyrrolidino / 485 / 499 / 508 / 512 / 521 /
528 / 545 / piperidino / 557 / 560 / 568 / 579 / 582)

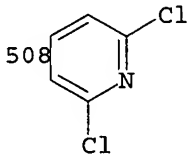


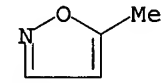


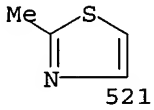


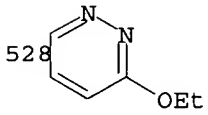


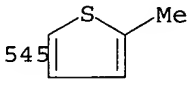


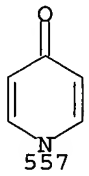


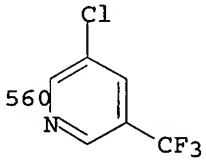


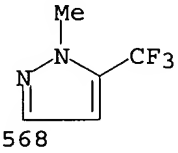


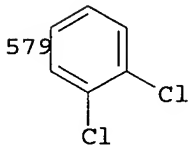


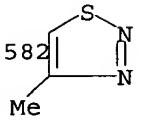












G38 = H / Me
G39 = H / Cl
Patent location: claim 1
Note: substitution is restricted
Note: or pharmaceutically acceptable salts, esters, amides, or prodrugs

L52 ANSWER 6 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:477959 MARPAT
TITLE: Preparation of tri-and bi-cyclic heteroaryl histamine-3 receptor ligands

INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang, Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser, Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005256309	A1	20051117	US 2004-844101	20040512
WO 2005113536	A2	20051201	WO 2005-US14866	20050429
WO 2005113536	A3	20060330		

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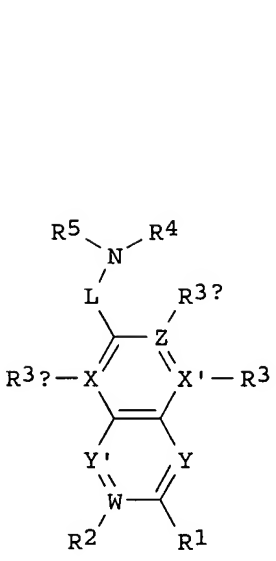
PRIORITY APPLN. INFO.: US 2004-844101 20040512
GI



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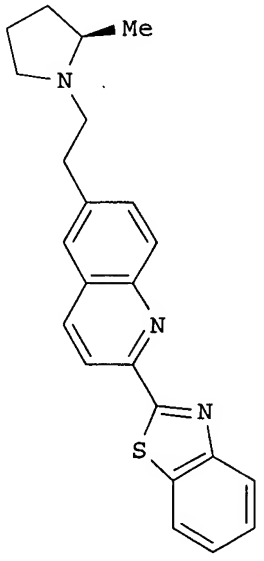
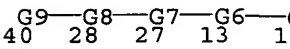


II

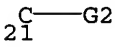
AB Title compds. I [Y and Y' independently = CH, CF, and N; X, X', Z and W independently = C or N; one of R1 and R2 is selected from L2R6 with the other of R1 and R2 = H, alkyl, alkoxy, etc.; L2 = O, CO, S, NH, etc.; R6 = bicyclic or tricyclic ring, each containing at least two heteroatoms; R3 = H, alkyl, alkoxy, halo, etc., or R3 is absent when X' = N; R3a = H, Me, alkoxy, halo, etc., or R3a is absent when Z = N; R3b = H, OH, alkyl, alkoxy, etc., or R3b is absent when X = N; R4 and R5 independently = alkyl, haloalkyl, hydroxyalkyl, etc.; or R4 and R5 taken together to form heterocyclic ring], and their pharmaceutically acceptable salts, are prepared and disclosed as useful in treating conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Thus, e.g., II was prepared via a multistep synthesis from (S)-Toluene-4-sulfonic acid 5-oxopyrrolidin-2-ylmethyl ester. In histamine-3 receptor binding studies, I demonstrated binding affinities from 810 nM to 0.02 nM. Also disclosed are pharmaceutical compns. comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing compds. within the scope of formula (I).

MSTR 1A

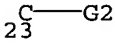


G1 = **N** / **11**

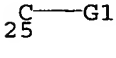
G2 = H / F
G3 = N / **21**



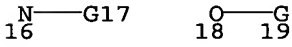
G4 = **N** / 23



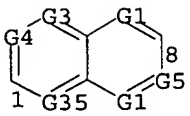
G5 = **N** / 25

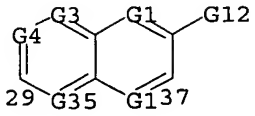


G6 = O / C(O) / S / alkylene <containing 1-4 C, unbranched> (opt. substd. by 1 or more G15) / G16 / **NH** / 16
/
18-27 19-15

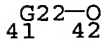


G7 = **1-28 8-13** / 29-28 37-13

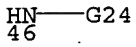


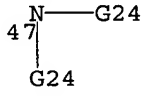


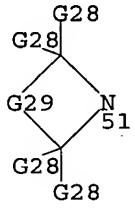
G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / **41-40 42-27**

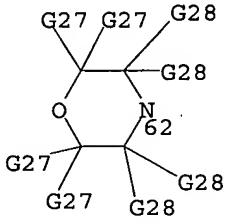


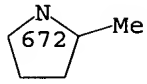
G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 672)



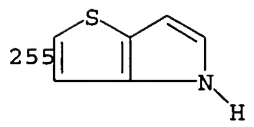


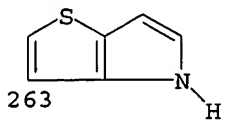


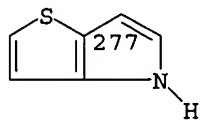


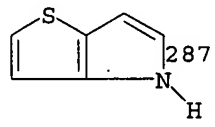


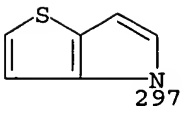
G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / aryl (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G14 = heterocycle <containing 2 or more heteroatoms,
zero or more N, zero or more O, zero or more S, 2-3 rings> /
(Specifically claimed: 255 / 263 / 277 / 287 / 297 / 309 /
319 / 330 / 344 / 351 / 364 / 374 / 382 / 390 / 401 / 417 /
429 / 437 / 446 / 458 / 461 / 473 / 481 / 489 / 500 / 514 /
benzothiazolyl / benzotriazolyl / 525 / 532 / 539 / 555 /
561 / 573 / 579 / 586 / 597 / 604 / 607 / 619 / 635 / 646 /
655 / 664 / quinoxalinyl / 680 / 697 / 711 / 714 / 725 /
736 / 753)







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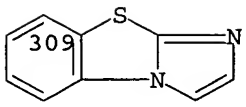
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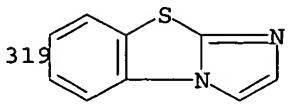
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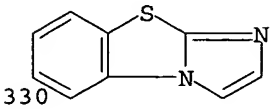
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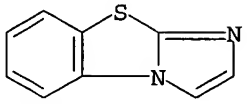
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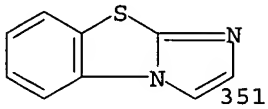
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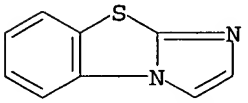
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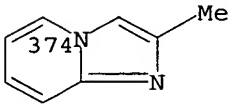
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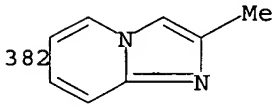
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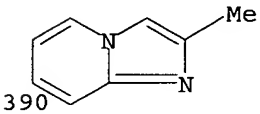
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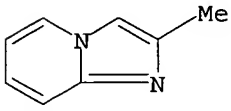
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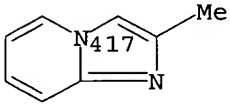
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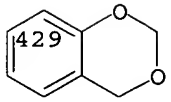
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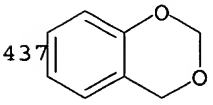
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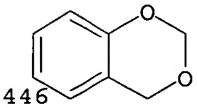
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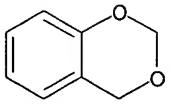
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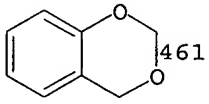
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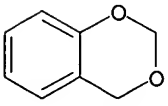
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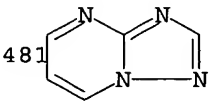
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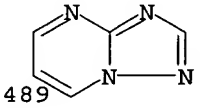
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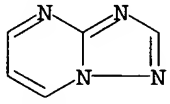
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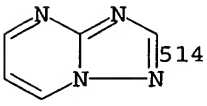
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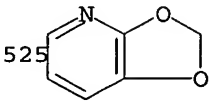
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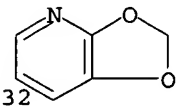
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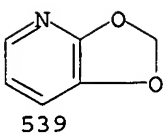
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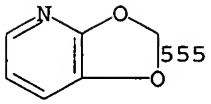
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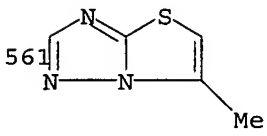
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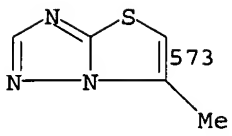
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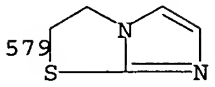
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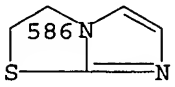
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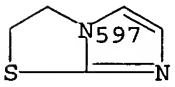
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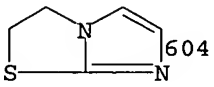
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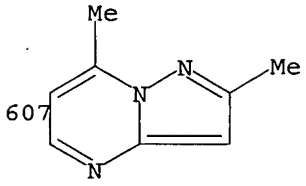
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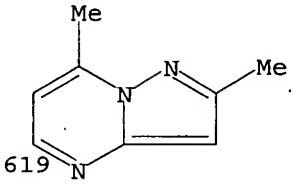
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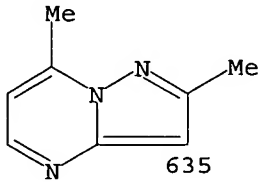
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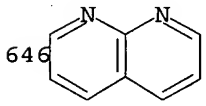
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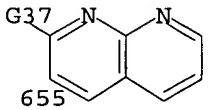
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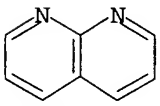
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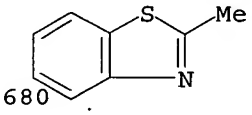
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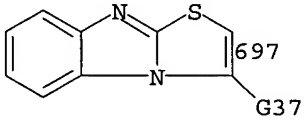
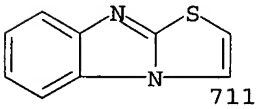

697 G37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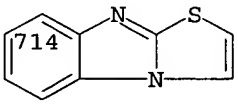
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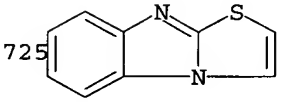
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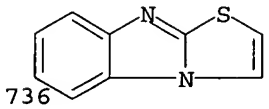
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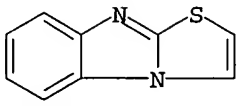
753

G15 = OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / F
G16 = (1-4) CH2
G17 = alkyl <containing 1-10 C>
G19 = alkylene <containing 1-4 C, unbranched> (opt. substd. by 1 or more G15) / G16

G20 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
I / CN
G22 = alkylene <containing 2-6 C>
(opt. substd. by 1 or more G10) / G23
G23 = (2-6) CH2
G24 = alkyl <containing 1-10 C>
(opt. substd. by 1 or more G25) /
cycloalkyl <containing 3-8 C>
G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F
G27 = H / OH / alkyl <containing 1-10 C>
(opt. substd. by OH) / F
G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F)
G29 = (1-5) 57

G30—C(57)——G30

G30 = H / OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F
G35 = N / **252**

C(252)——G36

G36 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
alkylthio <containing 1-10 C>
G37 = H / Me
Patent location: claim 1
Note: substitution is restricted
Note: or pharmaceutically acceptable salts, esters,
amides, or prodrugs

L52 ANSWER 7 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:477862 MARPAT
TITLE: Preparation of bicyclic amines bearing heterocyclic substituents as H3 receptor ligands
INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang, Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser, Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 41 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005256118	A1	20051117	US 2004-843742	20040512
WO 2005113551	A1	20051201	WO 2005-US14863	20050429

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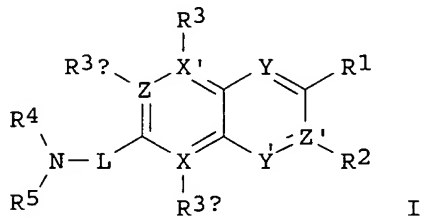
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-843742 20040512
GI



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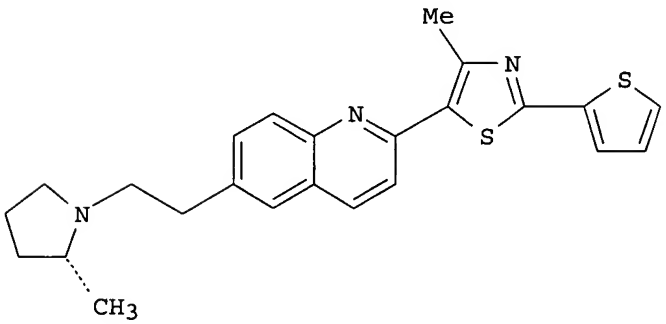
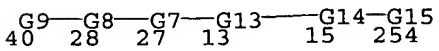


II

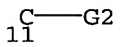
AB Title compds. I [Y, Y' = CH, CF, N; X, X', Z, Z' = C, N; R1, R2 = H, alkyl, alkoxy, aryl, cycloalkyl, etc.; R3 = absent when X' is N or H, alkyl, alkoxy, etc.; R3b = absent when Z is N or H, alkyl, alkoxy, halo, etc.; R4-5 = alkyl, haloalkyl, hydroxyalkyl, etc.; L = divalent alkyl, etc.] are prepared For instance, II is prepared in 7 steps from (S)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate, 1-(2-bromoethyl)-4-nitrobenzene, trimethylacetyl chloride, DMF and

1-(4-methyl-2-(thiophene-2-yl)thiazol-5-yl)ethanone. Representative compds. of the invention demonstrated binding affinities for the H3 receptor from about 810 nM to about 0.02 nM. I are useful for the treatment of conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Also disclosed are pharmaceutical compns. comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing compds. within the scope of formula (I).

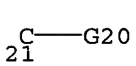
MSTR 1A



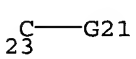
G1 = **N** / **11**



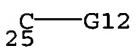
G2 = H / F
G3 = N / **21**



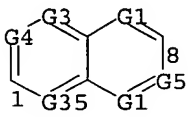
G4 = **N** / 23

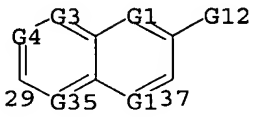


G5 = **N** / 25

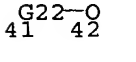


G7 = **1-28 8-13** / 29-28 37-13



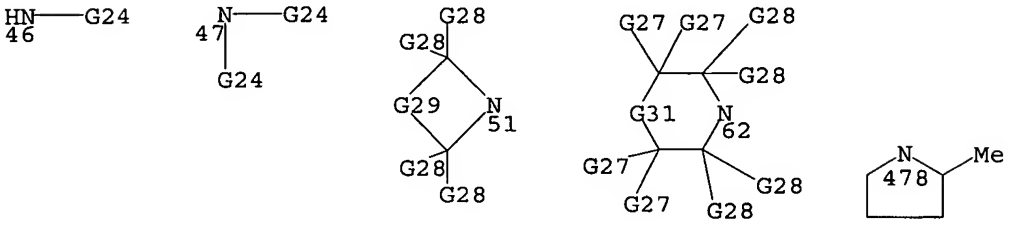


G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / **41-40 42-27**



G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms, 1-3 heteroatoms, 1 or more N, zero or more O, zero or more S (no other heteroatoms),

attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 478)



G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / aryl (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C> / (Specifically claimed: Me)
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd.) / **NH** / 16 / 18-27 19-15

G14 = any ring <containing 5-8 atoms, zero or more N,
zero or more O, zero or more S> /
(Specifically claimed: phenylene / 277-13 278-254 /
282-13 284-254 / 288-13 287-254 / 293-13 294-254 /
299-13 297-254 / 304-13 303-254 / 310-13 309-254 /
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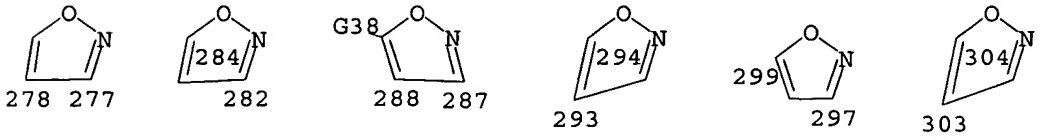
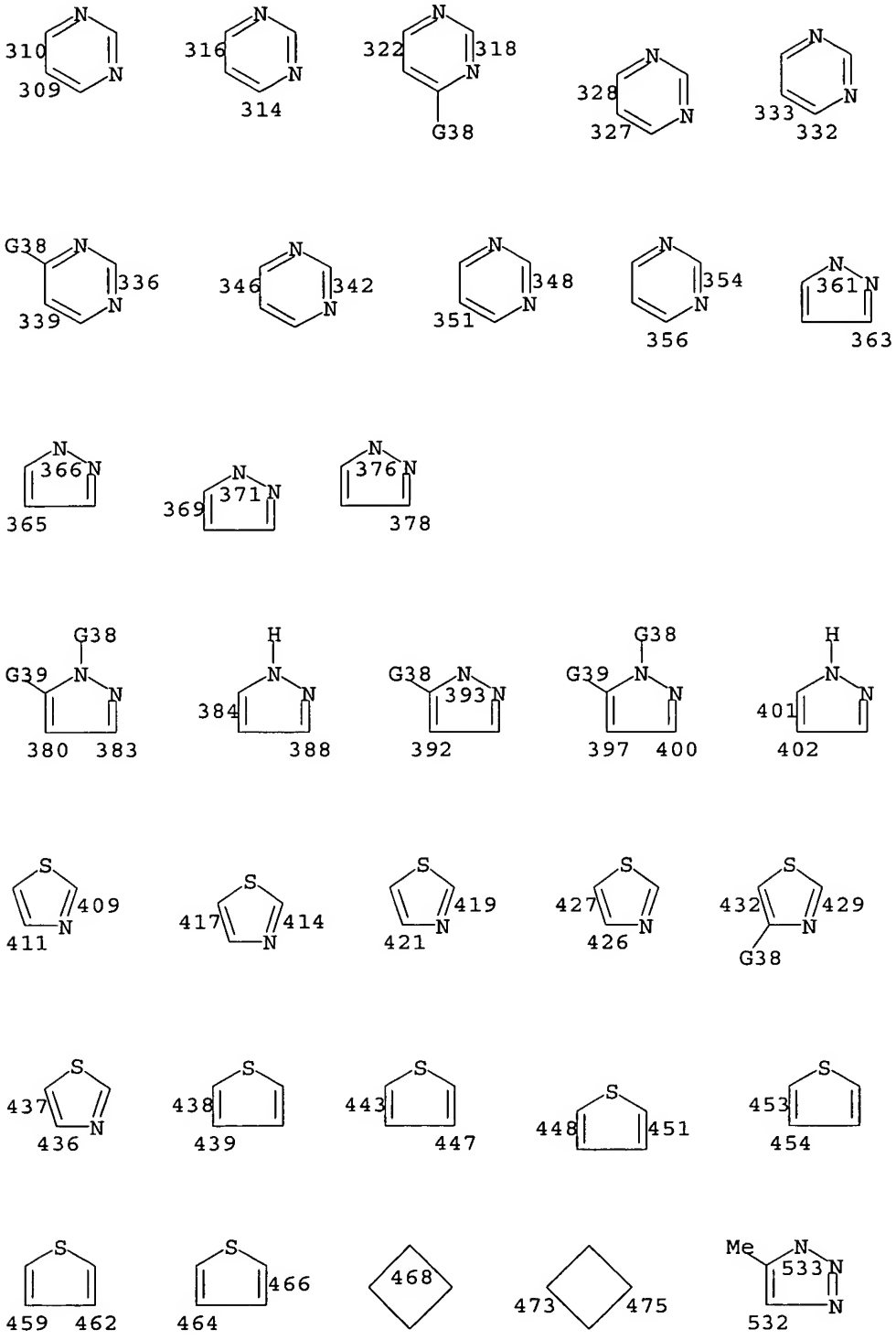
348-13 351-254 / 354-13 356-254 / 361-13 363-254 /
366-13 365-254 / 371-13 369-254 / 378-13 376-254 /
383-13 380-254 / 388-13 384-254 / 392-13 393-254 /
397-13 400-254 / 402-13 401-254 / 409-13 411-254 /
414-13 417-254 / 421-13 419-254 / 426-13 427-254 /
432-13 429-254 / 437-13 436-254 / 438-13 439-254 /
443-13 447-254 / 448-13 451-254 / 454-13 453-254 /
459-13 462-254 / 464-13 466-254 / 468 / 473-13 475-254 /
heterocycle <containing 5 atoms, 3 N, 2 C, aromatic,
2 double bonds, 5-membered monocyclic ring> /
532-13 533-254 / 538-13 539-254)




310
309
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G38
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333
332
G38
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363
366
365
369
371
376
378
G38
G39
380
383
H
384
388
G38
393
392
G38
G39
397
400
H
401
402
409
411
417
414
419
421
427
426
432
429
G38
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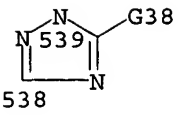
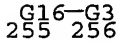
462
466
464
468
473
475
Me
533
532

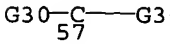


G15 = G37 / 255

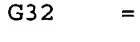


G16 = R <"linking group"> / (Specifically claimed: 271-15 272-256 / 273-15 274-256)

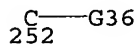
G17 = alkyl <containing 1-10 C>
G19 = alkylene <containing 1-4 C, unbranched> (opt. substd.)
G20 = H / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / F / Cl / Br / I / CN / alkylthio <containing 1-10 C>
G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br / I / CN
G22 = alkylene <containing 2-6 C> (opt. substd. by 1 or more G10) / G23
G23 = (2-6) CH2
G24 = alkyl <containing 1-10 C> (opt. substd. by 1 or more G25) / cycloalkyl <containing 3-8 C>
G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> / cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
G26 = H / alkyl <containing 1-10 C> (substd. by OH) / alkyl <containing 1-10 C> (substd. by 1 or more F) / OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> / dialkylamino <each alkyl containing 1-10 C> / F / alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C> / CONH2 / CHO / alkylaminocarbonyl <containing 1-10 C> / dialkylaminocarbonyl <each alkyl containing 1-10 C>
G27 = H / OH / alkyl <containing 1-10 C> (opt. substd. by OH) / F
G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) / alkyl <containing 1-10 C> (substd. by 1 or more F)
G29 = (1-5) 57



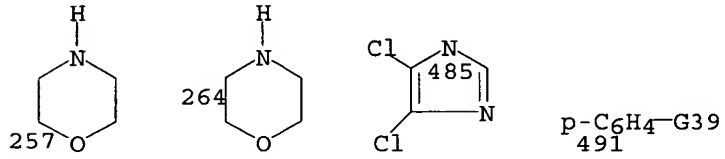
G30 = H / OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> / dialkylamino <each alkyl containing 1-10 C> / F
G31 = bond / O / S / 73

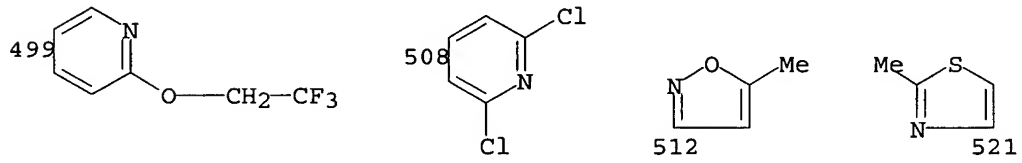


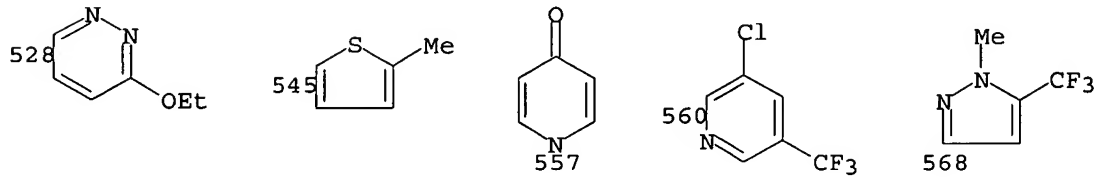
G32 = H / alkyl <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / CONH2 / CHO /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
G35 = N / **252**



G36 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
alkylthio <containing 1-10 C>
G37 = any ring <containing 5-8 atoms, zero or more N,
zero or more O, zero or more S> /
(Specifically claimed: isoxazolyl / morpholino / 257 / 264 /
491 / pyridazinyl / pyridyl / pyrimidinyl / pyrazinyl /
pyrazolyl / thiadiazolyl / thiazolyl / thienyl / triazolyl /
cyclobutyl / pyrrolidino / 485 / 499 / 508 / 512 / 521 /
528 / 545 / piperidino / 557 / 560 / 568 / 579 / 582)







G38 = H / Me
G39 = H / Cl
Patent location: claim 1
Note: substitution is restricted
Note: or pharmaceutically acceptable salts, esters, amides, or prodrugs

L52 ANSWER 8 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 141:71458 MARPAT
TITLE: Preparation of quinoline compounds for use in MCH receptor related disorders
INVENTOR(S): Frimurer, Thomas Michael; Ulven, Trond; Hoegberg, Thomas; Norregaard, Pja Karina; Little, Paul Brian; Receveur, Jean-Marie
PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.
SOURCE: PCT Int. Appl., 217 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004052370	A2	20040624	WO 2003-DK857	20031211
WO 2004052370	A3	20040819		
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2508681	AA	20040624	CA 2003-2508681	20031211
AU 2003287878	A1	20040630	AU 2003-287878	20031211
EP 1572212	A2	20050914	EP 2003-779716	20031211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
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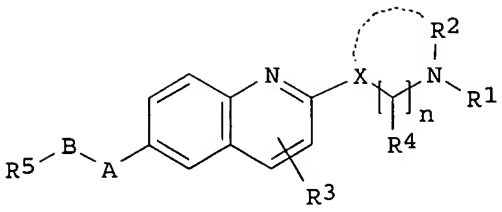
PRIORITY APPLN. INFO.:			DK 2002-1900	20021211
			WO 2003-DK857	20031211

GI



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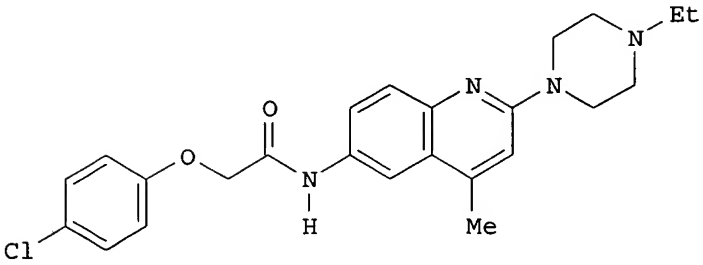
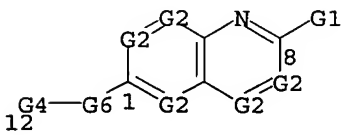


II

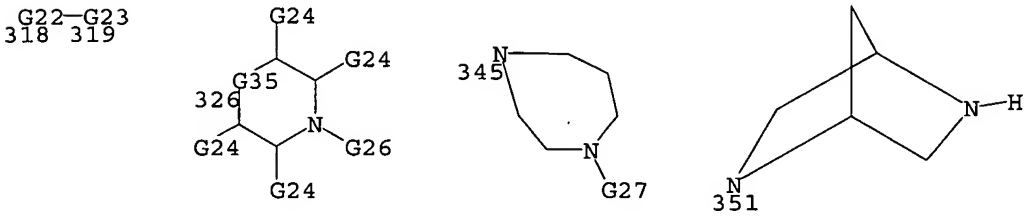
AB The present invention relates to the use of quinoline compds. I [A = CR7:CR7CONR7, YCR7CONR7, CONR7CONR7, etc. (wherein Y = CHR7, O, S, NR7; R7 = H, alkyl, alkenyl; R7 can be linked direct or via heteroatoms to B or the quinoline ring system when chemical feasible); X = N, C, O, S and X being restricted to N or C when linked to R2; B = (hetero)aryl; R1, R2 = H, alkyl, cycloalkyl, etc.; R4 = H, alkyl; R3 = H, alkyl, halo, etc.; R1, R2, R3 or R4 may optionally be linked to each other, or to the carbon chain linking the two N atoms, when possible, and O or NR1 may be inserted in the chain or ring; R4 may optionally be linked to X; R5 = H, halo, alkyl, etc.; n = 0-3; with provisos] for the preparation of a pharmaceutical and/or a cosmetic composition for the treatment, prophylaxis and/or diagnosis of a condition caused by or involving a melanin-concentrating hormone. The invention also relates to novel quinoline compds. per se. The synthesis of the compds. I and their intermediates is described in 184 synthetic examples. E.g., a 4-step synthesis of II, starting from 2-chlorolepidine and N-ethylpiperazine, which showed IC50 of 20 nM against MCH-1 receptor binding, was given. The quinoline compds. I have been found to interact with a melanin-concentrating hormone receptor, a MCH receptor. The compds. I have modulating activity on the MCH receptor such as e.g. antagonistic, agonistic or allosteric activity and are useful for medicinal or cosmetic purposes such as, e.g. in the treatment or prevention of feeding disorders like obesity, metabolic syndrome, Type II diabetes, bulimia, etc. or in the treatment or prevention of depression.

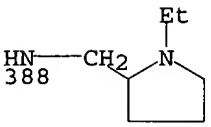
MSTR 1



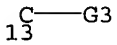
G1 = heterocycle <containing 5 or more atoms, 2 or more N, attached through 2 or more N>

(opt. substd. by G25) / **318** / (Specifically claimed: 326) /
(Examples: 345 / 351 / 388)

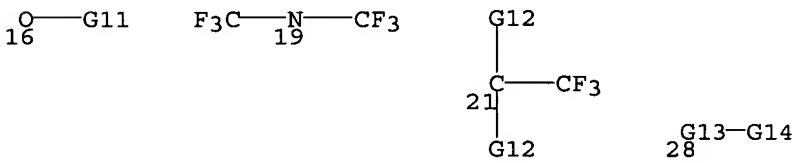




G2 = **N** / **13**



G3 = H / R / (Specifically claimed: Me) / (Example: Et)
G4 = aryl (opt. substd. by 1 or more G5) /
heteroaryl (opt. substd. by 1 or more G5) /
(Specifically claimed: Ph (opt. substd. by 1 or more G5) /
pyridyl (opt. substd. by 1 or more G5))
G5 = R / (Specifically claimed: halo /
alkyl <containing 1-6 C> / alkenyl <containing 2-6 C> /
alkynyl <containing 2-6 C> / cycloalkyl <containing 3-7 C>
(opt. substd. by G10) / 16 / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C> /
alkylcarbonylamino <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / 19 / SMe /
alkyl <containing 1-10 C> (substd. by 1 or more F) / CF3 /
28 / 21) / (Example: Cl)



G6 = 30-12 33-1 / 39-12 42-1 / **46-12 49-1** /
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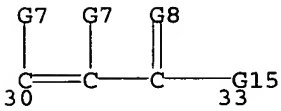
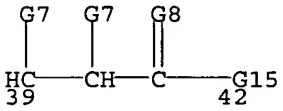
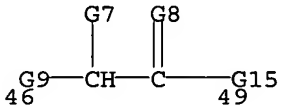
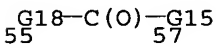
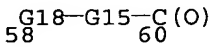
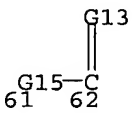


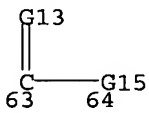


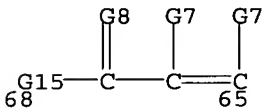


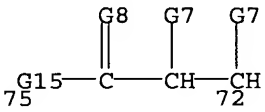


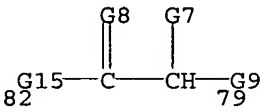


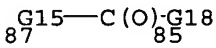


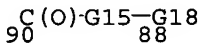


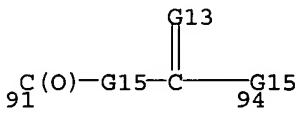


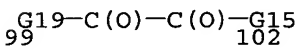


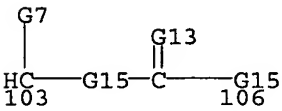


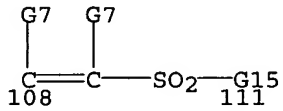


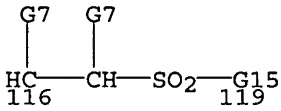


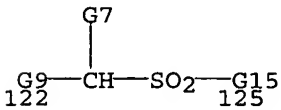


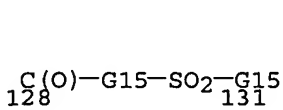


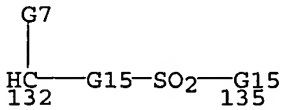


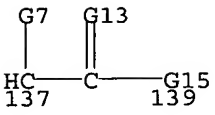


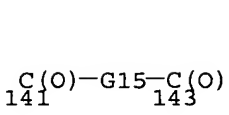


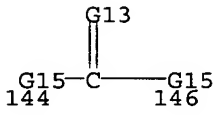


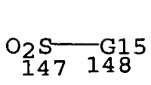


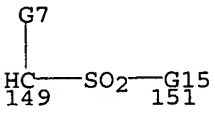


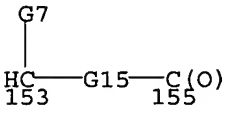

G7
G13
HC
C
G15
137
139

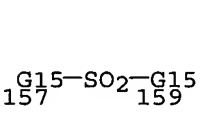

C(O)
G15
C(O)
141
143

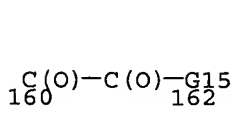

G13
G15
C
G15
144
146

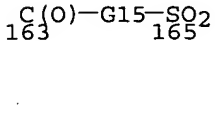

O2S
G15
147
148

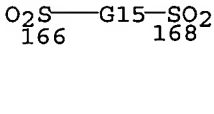

G7
HC
SO2
G15
149
151

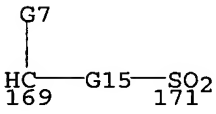

G7
HC
G15
C(O)
153
155

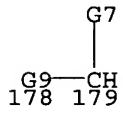

G15
SO2
G15
157
159

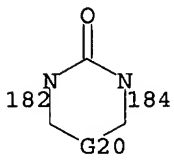

C(O)
C(O)
G15
160
162

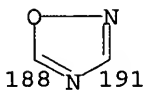

C(O)
G15
SO2
163
165

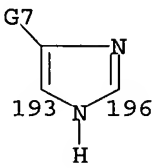

O2S
G15
SO2
166
168

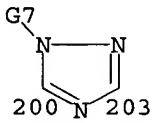

G7
HC
G15
SO2
169
171

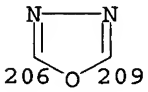

G7
G9
CH
178
179

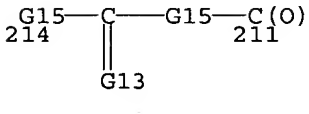

O
N
N
182
184
G20

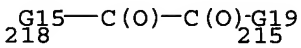

O
N
188
N
191

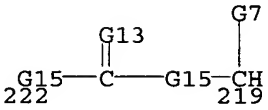

G7
N
193
N
196
H

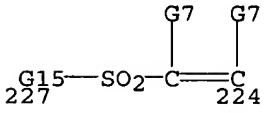

G7
N
N
200
N
203

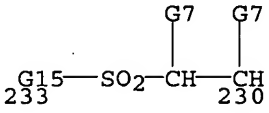

N
N
206
O
209

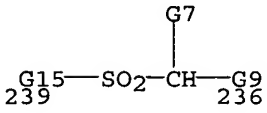

G15
C
G15
C(O)
214
211
G13

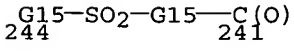

G15
C(O)
C(O)
G19
218
215

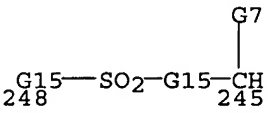

G7
G13
G15
C
G15
CH
222
219

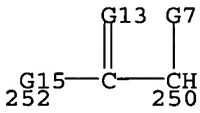

G7
G7
G15
SO2
C
C
227
224

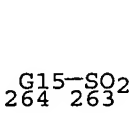

G7
G7
G15
SO2
CH
CH
233
230

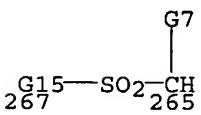

G7
G15
SO2
CH
G9
239
236

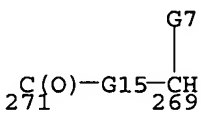

G15
SO2
G15
C(O)
244
241

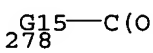

G7
G15
SO2
G15
CH
248
245

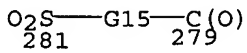

G13
G7
G15
C
CH
252
250

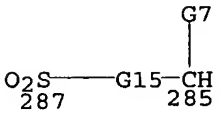

G15
SO2
264
263

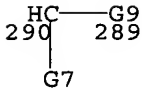

G7
G15
SO2
CH
267
265

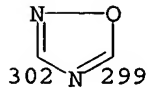

G7
C(O)
G15
CH
271
269

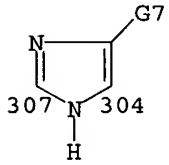

G15
C(O)
C(O)
278
276

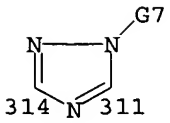

O2S
G15
C(O)
281
279

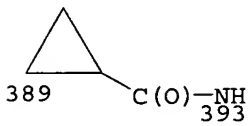




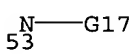




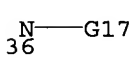




G7 = H / alkyl <containing 1-4 C> /
alkenyl <containing 2-4 C>
G8 = O / S
G9 = O / S / NH / 53

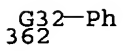


G10 = alkyl <containing 1-10 C>
G11 = alkyl <containing 1-10 C>
G12 = H / F
G13 = O / S
G14 = CF3 / alkyl <containing 1-10 C>
(substd. by 1 or more F)
G15 = NH / 36

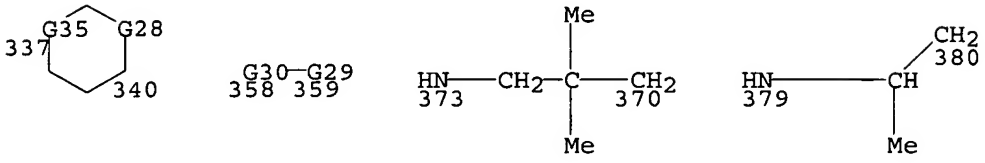


G17 = alkyl <containing 1-4 C> /
alkenyl <containing 2-4 C>
G18 = arylene / heteroarylene
G19 = 95 / O / S / NH / 97

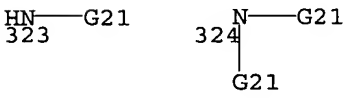
G20 = bond / CH2
G21 = alkenyl <containing 2-6 C> /
alkynyl <containing 2-6 C> / alkyl <containing 1-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-7 C>
(opt. substd. by G10) / alkyl <containing 1-10 C>
(substd. by 1 or more G33) / 362 /
(Specifically claimed: Me / Et / Pr-n / Bu-n / Pr-i / Bu-i /
cyclopentyl / Bu-t / Bu-s / CH2CH2OH)



G22 = heterocycle <containing 5 or more atoms, 1 or more N, attached through 1 or more N> (opt. substd. by G24) / **358-8 359-319** / (Specifically claimed: 337-8 340-319) / (Examples: 373-8 370-319 / 379-8 380-319)

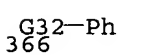


G23 = NH2 / 323 / 324 / (Examples: pyrrolidino / morpholino / piperidino)

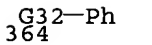


G24 = alkyl <containing 1-4 C> (opt. substd. by (1-2) alkyl <containing 1-4 C>) / (Example: Me)

G25 = alkenyl <containing 2-6 C> / alkynyl <containing 2-6 C> / alkyl <containing 1-6 C> (opt. substd. by OH) / cycloalkyl <containing 3-6 C> (opt. substd. by OH) / cycloalkyl <containing 3-7 C> (opt. substd. by G10) / alkyl <containing 1-10 C> (substd. by 1 or more G33) / 366



G26 = alkenyl <containing 2-6 C> / alkynyl <containing 2-6 C> / alkyl <containing 1-6 C> (opt. substd. by OH) / cycloalkyl <containing 3-6 C> (opt. substd. by OH) / cycloalkyl <containing 3-7 C> (opt. substd. by G10) / alkyl <containing 1-10 C> (substd. by 1 or more G33) / 364 / (Specifically claimed: alkyl <containing 1-6 C> (opt. substd. by OH) / cycloalkyl <containing 3-6 C> (opt. substd. by OH) / Me / Et / Pr-n / Bu-n / Pr-i / Bu-i / cyclopentyl / Bu-t / Bu-s / CH2CH2OH)

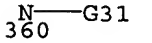


G27 = H / Me

G28 = CH2 / (Example: bond)

G29 = **G34** / alkylene <containing 1-3 C> (opt. substd. by alkyl <containing 1 or more C>)

G30 = **NH** / 360 / O / S / CH2 (opt. substd.)



G31 = R / (Example: Me)
G32 = (1-3) CH2
G33 = aryl / heteroaryl
G34 = **(0-3) CH2**
G35 = CH / N
Patent location: claim 1
Note: substitution is restricted
Note: additional derivatization also claimed

L52 ANSWER 9 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 141:7138 MARPAT
TITLE: Preparation of bicyclic-substituted amines as histamine-3 receptor ligands
INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang, Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser, Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill A.; Nersesian, Diana L.; Pu, Yu-Ming; Sharma, Padam N.; Bennani, Youssef L.; Curtis, Michael P.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 229 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004043458	A1	20040527	WO 2003-US335365	20031105
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004092521	A1	20040513	US 2002-292422	20021112
US 2004152704	A1	20040805	US 2003-689735	20031022
CA 2505427	AA	20040527	CA 2003-2505427	20031105
AU 2003291329	A1	20040603	AU 2003-291329	20031105
EP 1569637	A1	20050907	EP 2003-768721	20031105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006514926	T2	20060518	JP 2004-551799	20031105

PRIORITY APPLN. INFO.:
US 2002-292422 20021112
US 2002-425376P 20021112
US 2003-689735 20031022
WO 2003-US35365 20031105

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [wherein Y, and B = independently CH, CF, or N; X, A, Z, and C = independently C or N; one of R1 and R2 = halo, CN, aryl, aryloxy, etc.; the other of R1 and R2 = H, cyclo/alkyl, thio/alkoxy, aryl, halo, CN, provided that R2 is absent when C = N; R3 = H, alkyl, alkoxy, absent, etc.; R = absent, H, halo, Me, alkoxy, or CN; R6 = absent, H, alkyl, thio/alkoxy, halo, OH, CN; R4 and R5 = independently alkyl, haloalkyl, hydroxyalkyl, or NR4R5 = (un)1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, etc.; L = (un)substituted alkylene or -alkylene-O-; their pharmaceutically acceptable salts, esters, amides, or prodrugs] were prepared as histamine-3 receptor ligands. For example, quinoxaline II was prepared in 6 steps via cyclocondensation of benzenediamine III with glyoxal in EtOH, followed by reaction with oxo(phenyl)acetaldehyde. Selected I showed binding affinities of 0.12 to 20 nM towards histamine-3 receptors in rats. I are useful for the treatment of memory disorder, cognition disorder, obesity, etc. (no data).

MSTR 1A

```
 G9—G8—G7—G6
40  28  27  13
```

G1 = **N** / **11**

```
 C——G2
11
```

G2 = H / F
G3 = N / **21**

```
 C——G20
21
```

G4 = **N** / 23

```
 C——G21
23
```

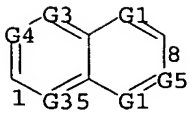
G5 = **N** / 25

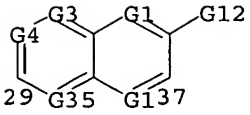
```
 C——G12
25
```

G6 = **14** / F / Cl / Br / I / CN

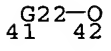
```
 G13—G14
14   15
```

G7 = **1-28 8-13** / 29-28 37-13

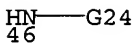


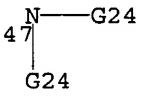


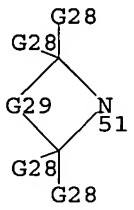
G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / **41-40 42-27**

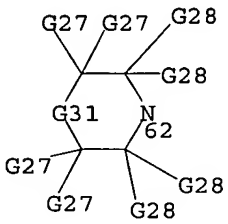


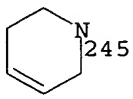
G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: pyrrolidino (opt. substd. by G41) /
245)







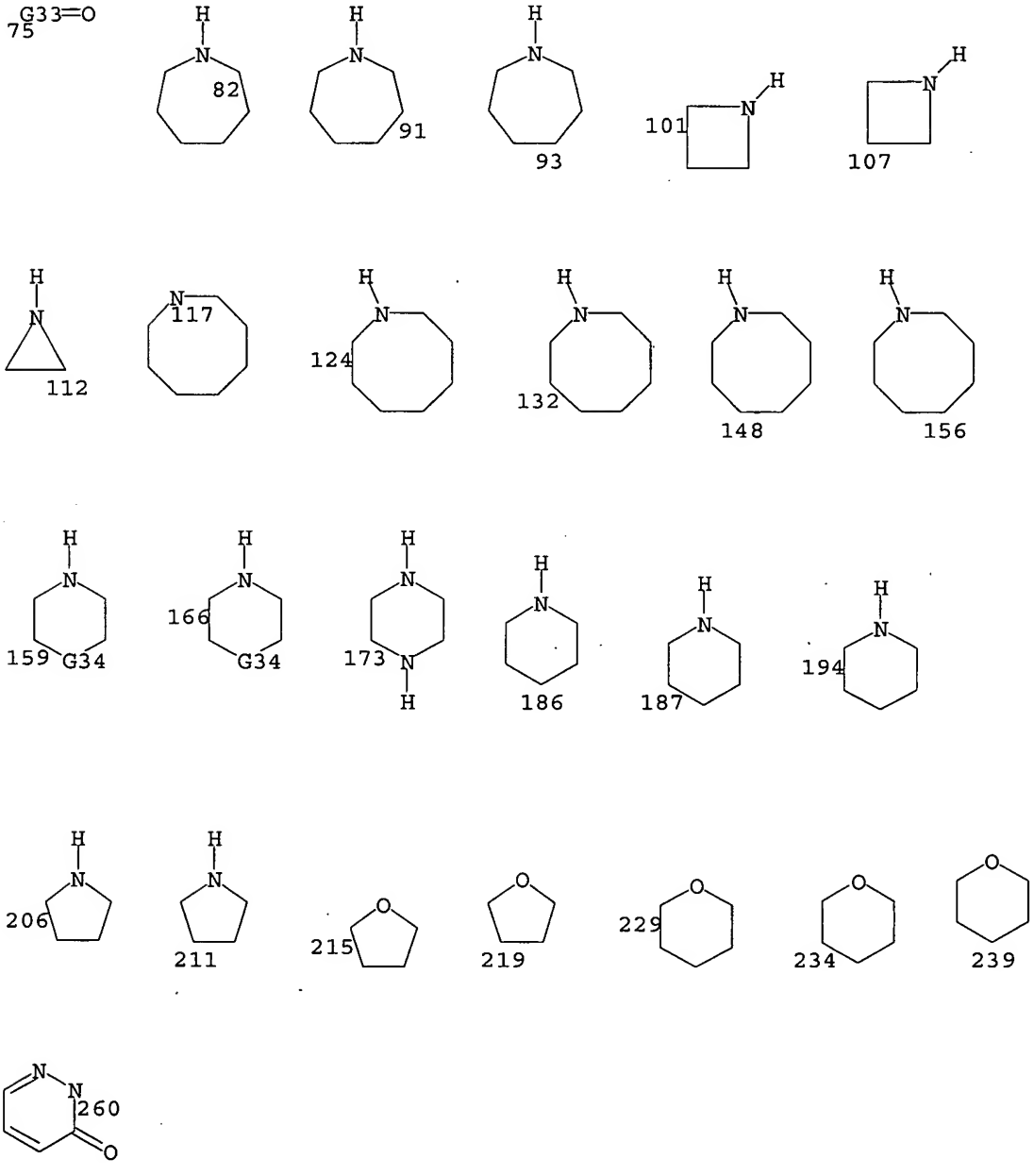




G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / Ph (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd. by 1 or more G15) / G16 / **NH** / 16
/
18-27 19-15 / (Specifically claimed: CHOH)

G14 = Ph (opt. substd. by G37) /
heteroaryl <containing 1-4 heteroatoms, zero or more N,
zero or more O, zero or more S (no other heteroatoms),
monocyclic> / heterocycle <containing 3-8 atoms,
1-3 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), monocyclic>
(opt. substd. by 1 or more G39) /
cycloalkyl <containing 3-8 C> /
(Specifically claimed: furyl / imidazolyl / isoxazolyl /
isothiazolyl / oxadiazolyl / oxazolyl / pyrazinyl /
pyrazolyl / pyridazinyl / 75 / pyridyl / pyrimidinyl /

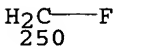
pyrrolyl / tetrazolyl / thiadiazolyl / thiazolyl / thienyl / triazinyl / triazolyl / hexahydroazepino / 82 / 91 / 93 / azetidino / 101 / 107 / aziridino / 112 / 117 / 124 / 132 / 148 / 156 / morpholino / 159 / 166 / piperazino / 173 / piperidino / 186 / 187 / 194 / pyrrolidino / 206 / 211 / heterocycle <containing 1 heteroatom, 1 N, 4 C, non-aromatic, 1 double-exact bond, 5-membered monocyclic ring> / thiomorpholino / 215 / 219 / 229 / 234 / 239 / 260)



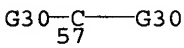
G15 = OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / F

G16 = (1-4) CH2

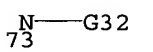
G17 = alkyl <containing 1-10 C>
G19 = alkylene <containing 1-4 C, unbranched>
(opt. substd. by 1 or more G15) / G16
G20 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
I / CN
G22 = alkylene <containing 2-6 C>
(opt. substd. by 1 or more G10) / G23
G23 = (2-6) CH2
G24 = alkyl <containing 1-10 C>
(opt. substd. by 1 or more G25) /
cycloalkyl <containing 3-8 C> / (Specifically claimed: Me /
Et / Pr-n)
G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F
G27 = H / OH / alkyl <containing 1-10 C>
(opt. substd. by OH) / F
G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F) /
(Specifically claimed: Me / Et / CH2OH / 250)



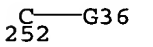
G29 = (1-5) 57



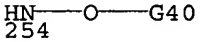
G30 = H / OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F
G31 = bond / O / S / 73



G32 = H / alkyl <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / CONH2 / CHO /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
G33 = heterocycle <containing 2 heteroatoms, 2 N, 4 C,
6-membered monocyclic ring>
G34 = O / S
G35 = N / **252**

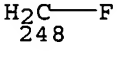


G36 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
alkylthio <containing 1-10 C>
G37 = R / CN / F / Cl / Br / I / NH2 (opt. substd.) /
alkoxy <containing 1-10 C> / alkyl <containing 1-10 C>
(opt. substd. by OH) / alkylcarbonyl <containing 1-10 C> /
alkoxycarbonyl <containing 1-10 C> /
cycloalkylcarbonyl <containing 3-8 C> /
alkylsulfonyl <containing 1-10 C> /
alkylthio <containing 1-10 C> /
alkyl <containing 1-10 C> (substd. by 1 or more G38)
G38 = F / Cl / Br / I
G39 = NH2 (opt. substd.) / F / Cl / Br / I /
alkyl <containing 1-10 C> (opt. substd. by 1 or more G38) /
CN / 254 / alkoxycarbonyl <containing 1-10 C> /
CONH2 (opt. substd.) / alkylcarbonyl <containing 1-10 C> /
alkoxy <containing 1-10 C>



254

G40 = alkyl <containing 1-10 C>
G41 = Me / Et / Pr-i / Bu-i / CH2OH / NHMe / NMe2 / 248



248

Patent location: claim 1
Note: substitution is restricted
Note: or pharmaceutically acceptable salts, esters, amides, or prodrugs

L52 ANSWER 10 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 140:105259 MARPAT
TITLE: Methods using a niclosamide compound and other agents for the treatment of neoplasms
INVENTOR(S): Lee, Margaret S.; Keith, Curtis; Auspitz, Benjamin A.; Zimmermann, Grant R.; Nichols, M. James; Foley, Michael A.
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004006906	A2	20040122	WO 2003-US22026	20030715
WO 2004006906	A3	20040304		

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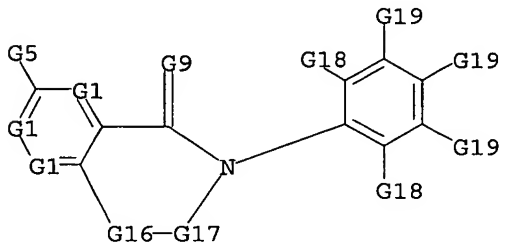
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003249244 A1 20040202 AU 2003-249244 20030715
PRIORITY APPLN. INFO.: US 2002-396135P 20020715
US 2002-396136P 20020715
US 2002-400913P 20020802
US 2002-400963P 20020802
US 2003-460203P 20030403
US 2003-460348P 20030403
WO 2003-US22026 20030715

AB The invention features a method for treating a patient having a cancer or other neoplasm by administering a niclosamide, or a structural or functional analog thereof, and, optionally, one or more antiproliferative agents in an amount effective to inhibit the growth of the neoplasm.

MSTR 1B



G1 = **N / 16**

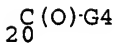
C—G2
16

G2 = H / OH / 18 / carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C> / F / Cl / Br / I / NO2

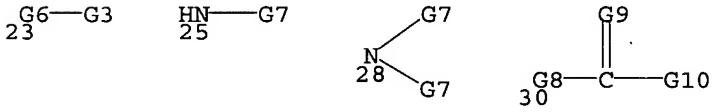
O—G3
18

G3 = 20 / carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl

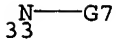
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>



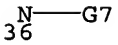
G4 = carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>
G5 = H / F / Cl / Br / I / OH / SH / 23 / NH2 / **25** / 28 /
30



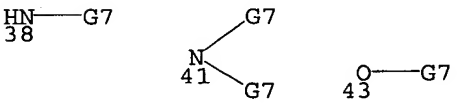
G6 = O / S
G7 = carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>
G8 = NH / 33



G9 = O / S / 36

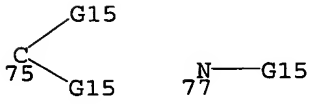


G10 = carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C> / NH2 / 38 / 41 / 43

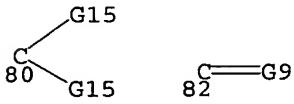


G15 = H / carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>

G16 = **75** / O / S / 77

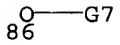


G17 = 80 / **82**

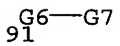


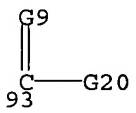
G18 = H / F / Cl / Br / I / CF3 / OH / 86 /
carbon chain <containing 1 or more C,

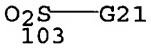
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>

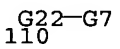


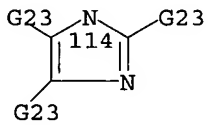
G19 = H / carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C> / F / Cl / Br / I / NO2 / CO2H /
SO3H / CF3 / CN / OH / SH / 91 / 93 / 103 / 110 / 114 / 120 /
127 / 134 / 145 / 155

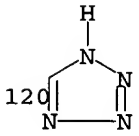


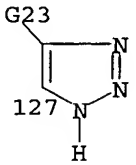


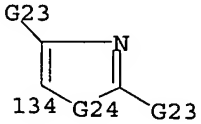


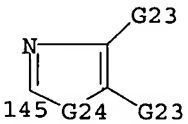


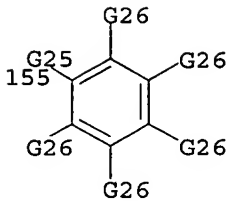




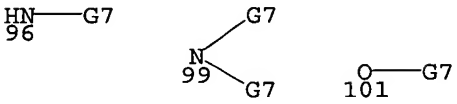




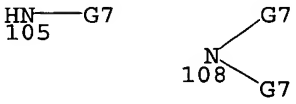




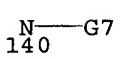
G20 = NH2 / 96 / 99 / 101



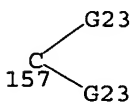
G21 = NH2 / 105 / 108



G22 = S(O) / SO2
G23 = H / F / Cl / Br / I / CN / NO2 / CF3 /
carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>
G24 = O / S / 140



G25 = O / S / 157



G26 = 2 or more H / F / Cl / Br / I / CN / NO2 / CF3 /
carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>

(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>
Patent location: claim 1
Note: or salts

L52 ANSWER 11 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 140:406732 MARPAT
TITLE: Preparation of pyrrolidine derivatives as histamine-3 receptor ligands
INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang, Sou-jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser, Gregory A.; Ku, Yi-yin; Liu, Huaqing; Lukin, Kirill A.; Nersesian, Diana L.; Pu, Yu-ming; Sharma, Padam N.; Bennani, Youssef L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 55 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004092521	A1	20040513	US 2002-292422	20021112
CA 2505427	AA	20040527	CA 2003-2505427	20031105
WO 2004043458	A1	20040527	WO 2003-US35365	20031105
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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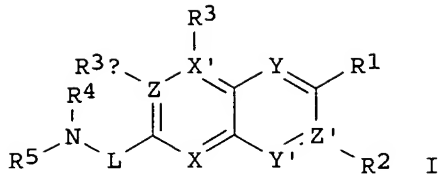
EP 1569637	A1	20050907	EP 2003-768721	20031105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006514926	T2	20060518	JP 2004-551799	20031105

PRIORITY APPLN. INFO.:
US 2002-292422 20021112
US 2002-425376P 20021112
US 2003-689735 20031022
WO 2003-US35365 20031105

GI



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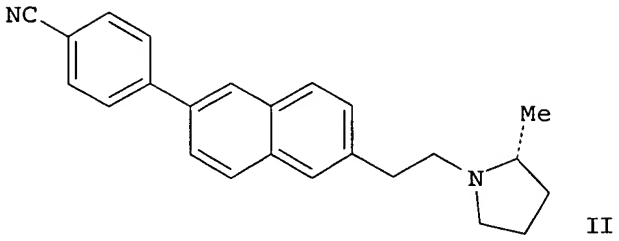


II

AB The title compds. I [wherein X, Y, and Y' = independently CH, CF, or N; X', Z, and Z' = independently C or N; R1 and R2 = independently halo, CN, H, alkyl, alkoxy, etc.; R3 = H, alkyl, alkoxy, absent, etc.; R3a = absent, H, halo, Me, alkoxy, or CN; R4 and R5 = independently alkyl, haloalkyl, hydroxyalkyl, etc.; L = (un)substituted alkylene or -alkylene-O-] or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof are prepared as histamine-3 receptor ligands. For example, the compound II was prepared in a multi-step synthesis. Some of compds. I showed binding affinities of 0.12 to 20 nM towards histamine-3 receptors in rat. I are useful for the treatment of memory disorder, cognition disorder, obesity, etc. (no data).

MSTR 1A

G9—G8—G7—G6
40 28 27 13

G1 = **N** / **11**

C—G2
11

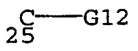
G2 = H / F
G3 = N / **21**

C—G20
21

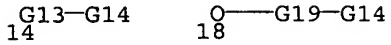
G4 = **N** / 23

C—G21
23

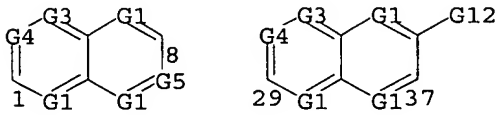
G5 = **N** / 25



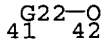
G6 = **14** / 18 / F / Cl / Br / I / CN



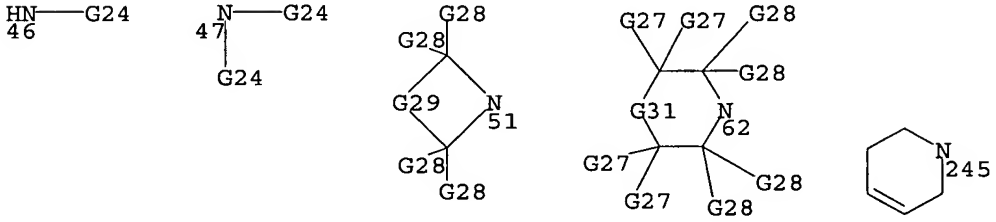
G7 = **1-28 8-13** / 29-28 37-13



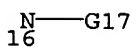
G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / **41-40 42-27**



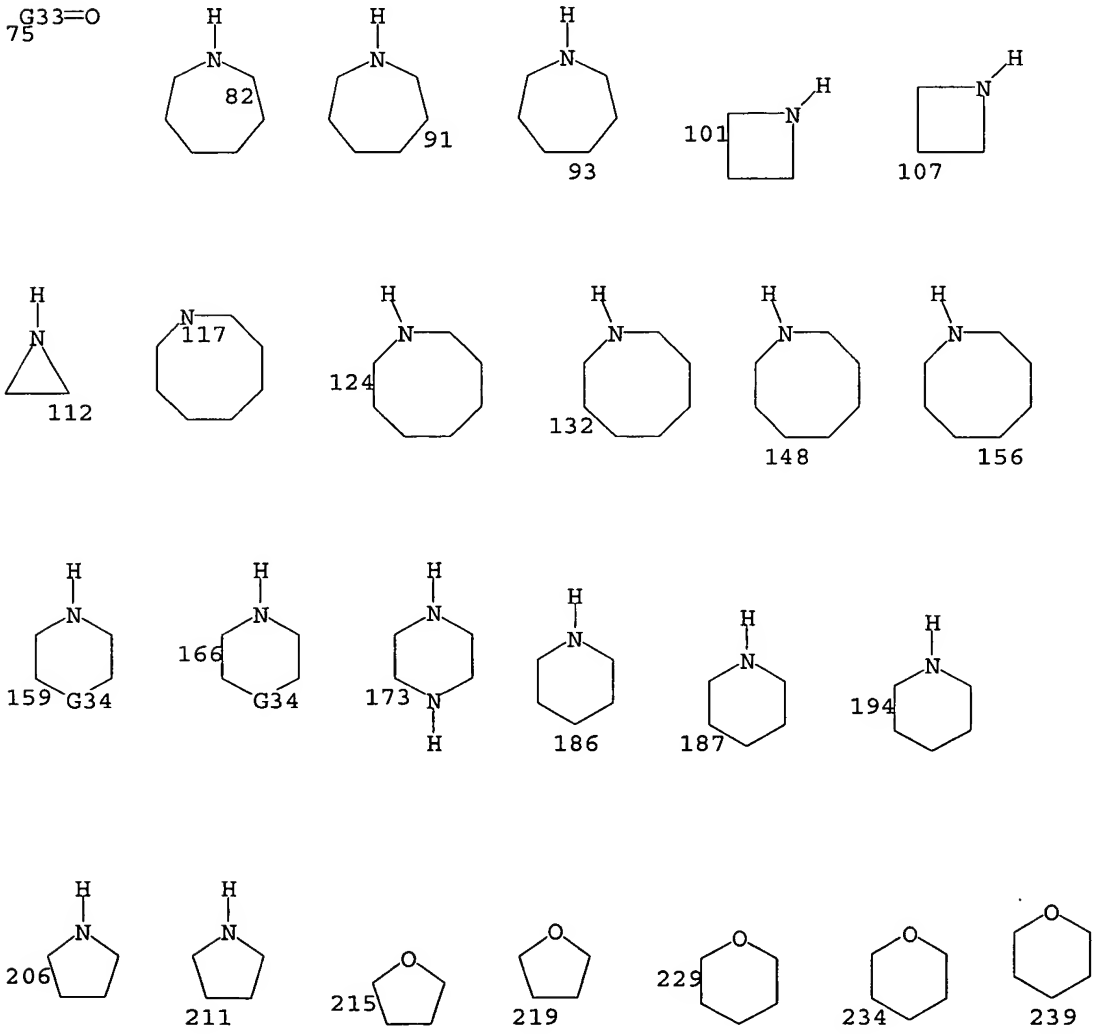
G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 245 / pyrrolidino (opt. substd. by
G35))



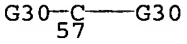
G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / Ph (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd. by 1 or more G15) / G16 / **NH** / 16



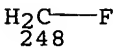
G14 = Ph (opt. substd. by G36) /
heteroaryl <containing 1-4 heteroatoms, zero or more N,
zero or more O, zero or more S (no other heteroatoms),
monocyclic> / heterocycle <containing 3-8 atoms,
1-3 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), monocyclic> /
cycloalkyl <containing 3-8 C> /
(Specifically claimed: furyl / imidazolyl / isoxazolyl /
isothiazolyl / oxadiazolyl / oxazolyl / pyrazinyl /
pyrazolyl / pyridazinyl / 75 / pyridyl / pyrimidinyl /
pyrrolyl / tetrazolyl / thiadiazolyl / thiazolyl / thienyl /
triazinyl / triazolyl / hexahydroazepino / 82 / 91 / 93 /
azetidino / 101 / 107 / aziridino / 112 / 117 / 124 / 132 /
148 / 156 / morpholino / 159 / 166 / piperazino / 173 /
piperidino / 186 / 187 / 194 / pyrrolidino / 206 / 211 /
heterocycle <containing 1 heteroatom, 1 N, 4 C,
non-aromatic, 1 double-exact bond,
5-membered monocyclic ring> / thiomorpholino / 215 / 219 /
229 / 234 / 239)



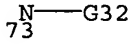
G15 = OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / F
G16 = (1-4) CH2
G17 = alkyl <containing 1-10 C>
G19 = alkylene <containing 1-4 C, unbranched> (opt. substd. by 1 or more G15) / G16
G20 = H / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / F / Cl / Br / I / CN / alkylthio <containing 1-10 C>
G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br / I / CN
G22 = alkylene <containing 2-6 C> (opt. substd. by 1 or more G10) / G23
G23 = (2-6) CH2
G24 = alkyl <containing 1-10 C> (opt. substd. by 1 or more G25) / cycloalkyl <containing 3-8 C> / (Specifically claimed: Me / Et / Pr-i)
G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> / cycloalkyl <containing 3-8 C>
G26 = H / alkyl <containing 1-10 C> (substd. by OH) / alkyl <containing 1-10 C> (substd. by 1 or more F) / OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> / dialkylamino <each alkyl containing 1-10 C>
G27 = H / OH / alkyl <containing 1-10 C> (opt. substd. by OH) / F
G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) / alkyl <containing 1-10 C> (substd. by 1 or more F)
G29 = (1-5) 57



G30 = H / OH / alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> / dialkylamino <each alkyl containing 1-10 C> / F / (Specifically claimed: Me / Et / Pr-i / Bu-i / CH2OH / NHMe / NMe2 / 248)



G31 = bond / O / S / 73



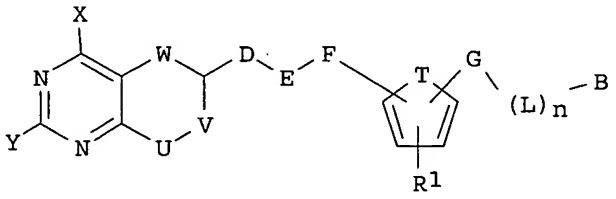
G32 = H / alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C> / CONH2 / CHO / alkylaminocarbonyl <containing 1-10 C> / dialkylaminocarbonyl <each alkyl containing 1-10 C>
G33 = heterocycle <containing 2 heteroatoms, 2 N, 4 C, 6-membered monocyclic ring>
G34 = O / S
G35 = Me / Et / Pr-i / Bu-i / CH2OH / 250

G36 = R / Cl / CN / F / SMe
Patent location: claim 1
Note: substitution is restricted
Note: or pharmaceutically acceptable salts, esters, amides, or prodrugs

L52 ANSWER 12 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:338133 MARPAT
TITLE: Preparation of folate mimetics and folate-receptor binding conjugates thereof
INVENTOR(S): Green, Mark A.; Leamon, Christopher P.; Ke, Chun-Yen
PATENT ASSIGNEE(S): Purdue Research Foundation, USA; Endocyte, Inc.
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002085908	A1	20021031	WO 2002-US13045	20020424
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1389209	A1	20040218	EP 2002-731495	20020424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004242582	A1	20041202	US 2004-475876	20040621
US 2005227985	A9	20051013		
PRIORITY APPLN. INFO.:			US 2001-286082P	20010424
			WO 2002-US13045	20020424

GI



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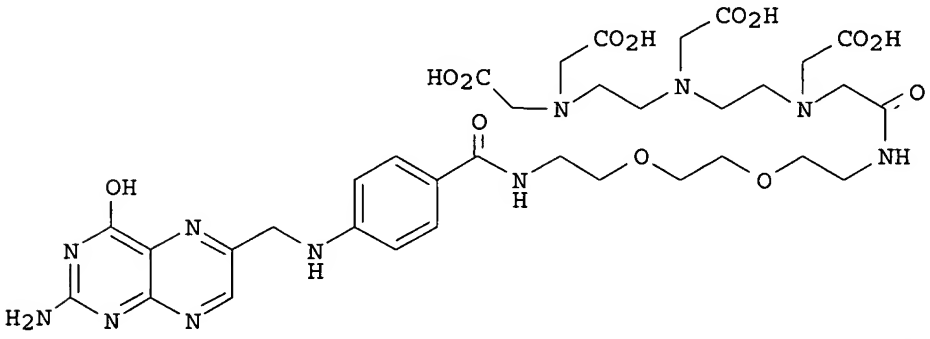
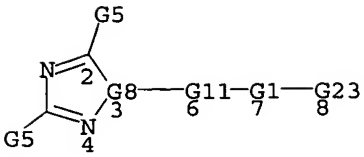


II

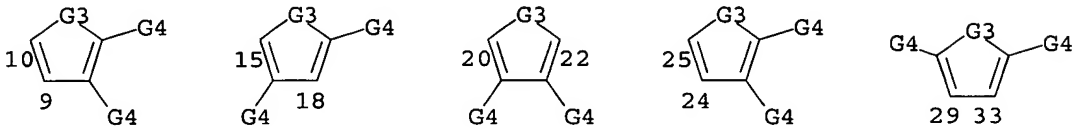
AB A cell population expressing folate receptors is selectively targeted with folate mimetic I [D = (CR6R7)s; E = (A1)p; F = (CR6R7)1-s; G = (A2)r; X, Y = halo, R2, OR2, SR3, NR4R5; U, V, W = (R6')C:, N:, (R6')C(R7'), N(R4'); T = S, O, N, C:C (such that T is part of an aromatic ring); A1, A2 = C(Z), C(Z)O, OC(Z), N(R4''), C(Z)N(R4''), N(R4'')C(Z), OC(Z)N(R4''), N(R4'')C(Z)O, N(R4'')C(Z)N(R5''), O, S, S(O), SO2, N(R4'')SO2, C(R6'')C(R7''), N(C.tplbond.CH), N(CH2C.tplbond.CH), C1-12-alkyl, C1-12-alkoxy; Z = O, S; R1 = H, halo, C1-12-alkyl, C1-12-alkoxy; R2 - R5, R4', R4'' - R7'' = H, halo, C1-12-alkyl, C1-12-alkoxy, C1-12-alkenyl, C1-12-alkynyl, (C1-12-alkoxy)carbonyl, (C1-12-alkylamino)carbonyl; R6, R7 = H, halo, C1-12-alkyl, C1-12-alkoxy; R6R7 = O; R6', R7' = H, halo, C1-12-alkyl, C1-12-alkoxy; R6'R7' = O; L = divalent linker (with the proviso that L ≠ naturally occurring amino acid covalently linked to A2 at its α-amino group through an amide bond); n, p, r, s = 0, 1; B = H, leaving group]. Thus, CYK4-013 (II) was prepared from pteroic acid via coupling with (CH2OCH2CH2NH2)2 using PyBOP, HOBt and N-methylmorpholine in DMSO, followed by addition of DTPA tris(tert-butyl) ester. The folate mimetic is conjugated to a diagnostic or therapeutic agent to enable selective delivery of the agent to the targeted cell population. The 111In complex of II was selectively localized in the folate-receptor-pos. tumor xenografts of human KB cells in athymic mice (NuNu strain) and afforded prolonged tumor retention of 111In (5.4, 5.5, and 3.6% ID/g at 1 h, 4 h, and 24 h, resp.); blockable binding was also observed in the kidneys, where the folate receptor occurs in the proximal tubes.

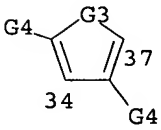
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

MSTR 1

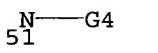


G1 = phenylene (opt. substd. by 1 or more G2) /
10-6 9-8 / 15-6 18-8 / 20-6 22-8 / 24-6 25-8 /
29-6 33-8 / 34-6 37-8

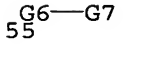




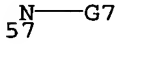
G2 = F / Cl / Br / I / At / alkyl <containing 1-12 C> /
alkoxy <containing 1-12 C> / (Specifically claimed: Me)
G3 = S / O / 51



G4 = H / F / Cl / Br / I / At /
alkyl <containing 1-12 C> / alkoxy <containing 1-12 C> /
(Specifically claimed: Me)
G5 = F / Cl / Br / I / At / H /
alkyl <containing 1-12 C> / alkoxy <containing 1-12 C> /
CHO / alkylcarbonyl <containing 1-11 C> /
alkenyl <containing 2-12 C> / alkynyl <containing 2-12 C> /
alkoxycarbonyl <containing 1-12 C> /
alkylaminocarbonyl <containing 1-12 C> /
dialkylaminocarbonyl <each alkyl containing 1-12 C> / **55** /
(Specifically claimed: Me)



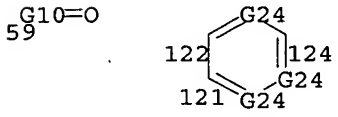
G6 = O / S / **57**



G7 = H / F / Cl / Br / I / At /
alkyl <containing 1-12 C> / alkoxy <containing 1-12 C> /

CHO / alkylcarbonyl <containing 1-11 C> /
alkenyl <containing 2-12 C> / alkynyl <containing 2-12 C> /
alkoxycarbonyl <containing 1-12 C> /
alkylaminocarbonyl <containing 1-12 C> /
dialkylaminocarbonyl <each alkyl containing 1-12 C> /
(Specifically claimed: Me)

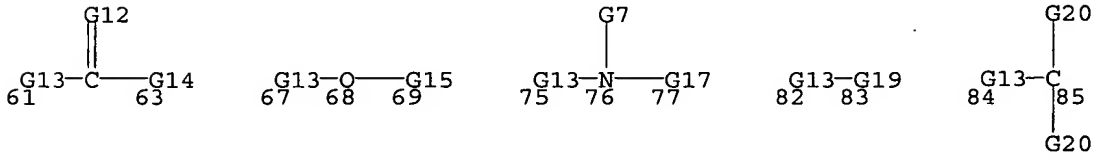
G8 = any ring <containing 0-3 heteroatoms,
0-3 N (no other heteroatoms), 3 or more C,
1 or more double bonds, attached through 3 or more C,
6-membered monocyclic ring> (opt. substd. by 1 or more G9) /
59 / **(Specifically claimed: 122-2 121-4 124-6)**

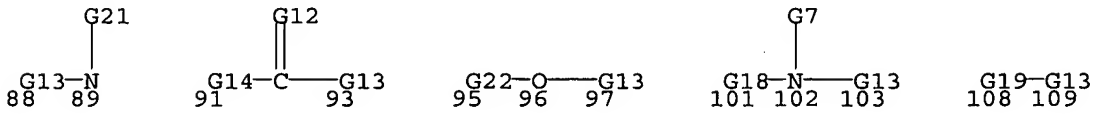


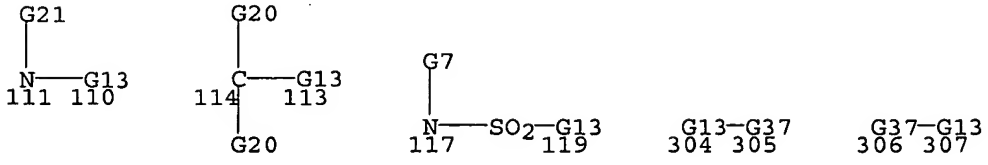
G9 = F / Cl / Br / I / At / alkyl <containing 1-12 C> /
alkoxy <containing 1-12 C> / CHO /
alkylcarbonyl <containing 1-11 C> /
alkenyl <containing 2-12 C> / alkynyl <containing 2-12 C> /
alkoxycarbonyl <containing 1-12 C> /
alkylaminocarbonyl <containing 1-12 C> /
dialkylaminocarbonyl <each alkyl containing 1-12 C>

G10 = any ring <containing 0-2 heteroatoms,
0-2 N (no other heteroatoms), 4 or more C,
1 or more double bonds, attached through 4 or more C,
6-membered monocyclic ring> (opt. substd.)

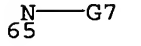
G11 = CH2 (opt. substd.) / C(O) / **61-3 63-7** /
67-3 69-7 / 75-3 77-7 / 82-3 83-7 / 84-3 85-7 /
88-3 89-7 / 91-3 93-7 / 95-3 97-7 / 101-3 103-7 /
108-3 109-7 / 111-3 110-7 / 114-3 113-7 / 117-3 119-7 /
304-3 305-7 / 306-3 307-7 / 308-3 310-7 / 311-3 313-7 /
314-3 316-7 / 317-3 319-7



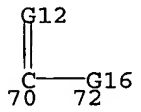




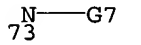
G12 = O / S
G13 = CH2 (opt. substd.) / C(O)
G14 = bond / O / 65



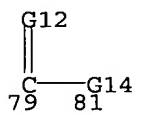
G15 = 70-68 72-7 / bond



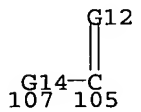
G16 = bond / 73



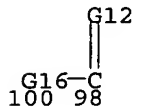
G17 = bond / 79-76 81-7 / SO2



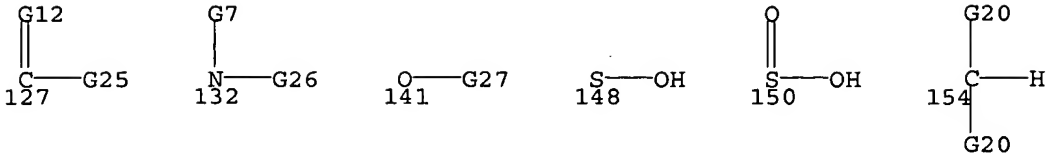
G18 = bond / 107-3 105-102

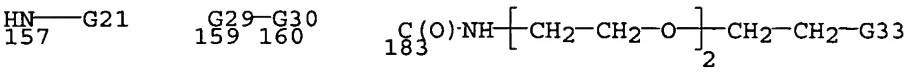


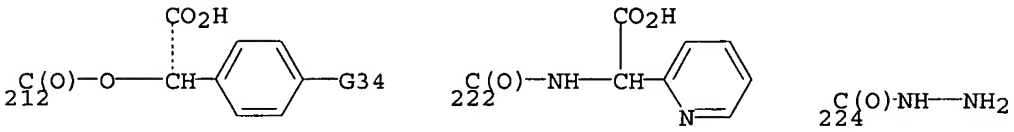
G19 = S / S(O) / SO2
G20 = H / R / (Specifically claimed: Me)
G21 = ethynyl / propargyl
G22 = 100-3 98-96 / bond

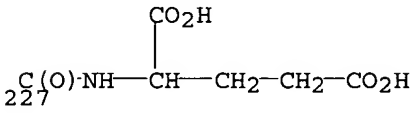


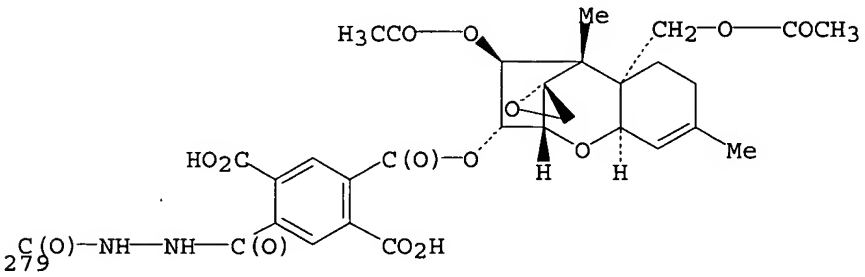
G23 = H / R <"leaving or linking group,
or diagnostic or therapeutic agent"> / 127 / 132 / 141 / SH /
148 / 150 / 154 / 157 / alkyl <containing 1-12 C>
(opt. substd. by OH) / alkoxy <containing 1-12 C> / 159 /
(Examples: 183 / 212 / 222 / 224 / 227 / 279)



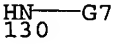




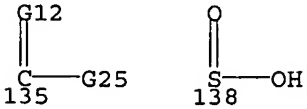




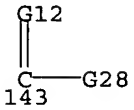
G24 = **CH** / **N**
G25 = H / OH / 130



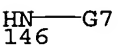
G26 = H / 135 / 138



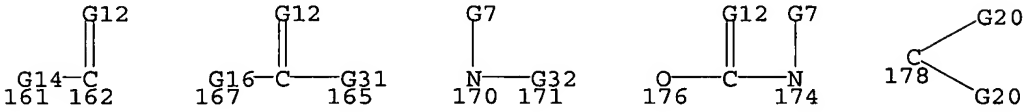
G27 = 143 / H

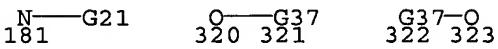


G28 = H / 146



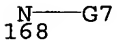
G29 = 161-7 162-160 / 167-7 165-160 / 170-7 171-160 / 176-7 174-160 / O / S / S(O) / SO2 / 178 / 181 / alkylene <containing 1-12 C> / 320-7 321-160 / 322-7 323-160





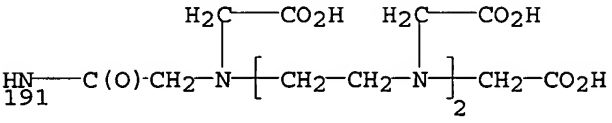
G30 = R <"leaving or linking group, or diagnostic or therapeutic agent">

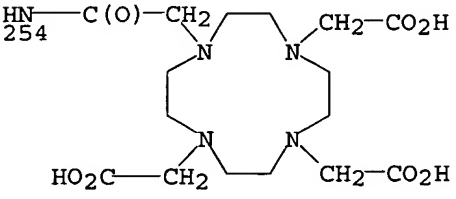
G31 = O / 168



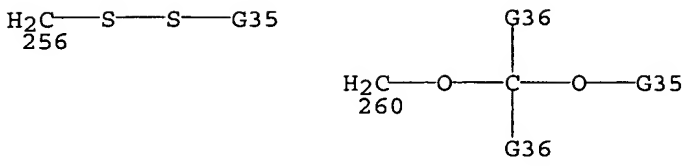
G32 = bond / SO2

G33 = 191 / 254





G34 = H / 256 / 260



G35 = R <"drug or drug bearing moiety">
G36 = H / alkyl / cycloalkyl / Ph (substd.)
G37 = alkylene <containing 1-12 C>
Patent location: claim 1
Note: also incorporates claim 9
Note: substitution is restricted

L52 ANSWER 13 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 132:30857 MARPAT
TITLE: Heterocyclic compound inhibitors of p38 kinase, pharmaceutical compositions, and therapeutic use
INVENTOR(S): Salituro, Francesco; Bemis, Guy; Cochran, John
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964400	A1	19991216	WO 1999-US12951	19990611
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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EP 1086085	A1	20010328	EP 1999-927377	19990611
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EP 1277740	A1	20030122	EP 2002-22891	19990611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
US 2001025044	A1	20010927	US 2000-734069	20001211
US 6528508	B2	20030304		
US 2003149037	A1	20030807	US 2002-327020	20021220
US 6800626	B2	20041005		
US 2005049251	A1	20050303	US 2004-951409	20040927

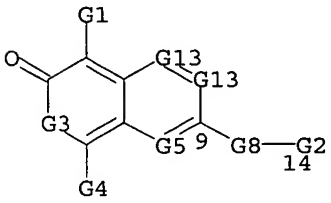
PRIORITY APPLN. INFO.:	
US 1998-89147P	19980612
EP 1999-927377	19990611
WO 1999-US12951	19990611
US 2000-734069	20001211
US 2002-327020	20021220

AB The invention relates to heterocyclic compound inhibitors of p38, a

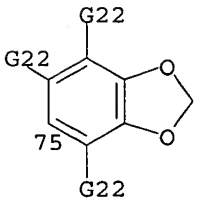
mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compns. comprising the inhibitors of the invention and methods of utilizing those compns. in the treatment and prevention of various disorders.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

MSTR 1A



G1 = Ph (opt. substd.) / heterocycle <containing 5-6 atoms, aromatic, 5- to 6-membered monocyclic ring> (opt. substd.) / aryl <containing 8-10 C, bicyclic> (opt. substd.) / heterocycle <containing 8-10 atoms, aromatic, bicyclic> (opt. substd.) / (Specifically claimed: Ph (opt. substd. by (1-3) G17) / pyridyl (opt. substd. by (1-3) G17) / 75)

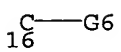


G2 = Ph (opt. substd.) / heterocycle <containing 5-6 atoms, aromatic, 5- to 6-membered monocyclic ring> (opt. substd.) / aryl <containing 8-10 C, bicyclic> (opt. substd.) / heterocycle <containing 8-10 atoms, aromatic, bicyclic> (opt. substd.) / (Specifically claimed: Ph (opt. substd. by (1-3) G20) / pyridyl (opt. substd. by (1-3) G20))

G3 = O / **NH (opt. substd.)**

G4 = H / alkyl <containing 1-3 C> / OH / alkoxy <containing 1-3 C>

G5 = **N** / 16

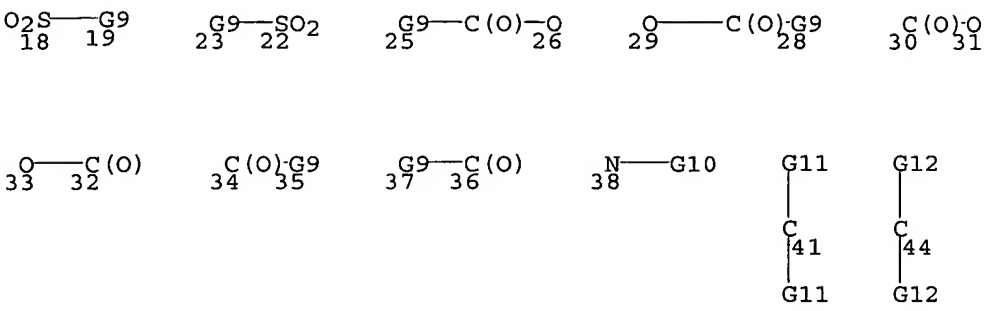


G6 = H / alkyl <containing 1-3 C> / alkenyl <containing 2-3 C> / alkynyl <containing 2-3 C> / Ph (opt. substd. by (1-3) G7)

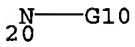
G7 = halo / OMe / CN / NO2 / NH2 / OH / Me / Et

G8 = S / O / SO2 / S(O) / **18-9 19-14** / 23-9 22-14 /

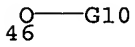
25-9 26-14 / 29-9 28-14 / C(O) / 30-9 31-14 /
33-9 32-14 / 34-9 35-14 / 37-9 36-14 / NH / 38 / 41 / 44



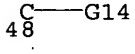
G9 = **NH** / 20



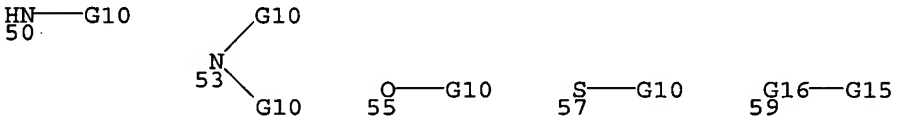
G10 = alkyl <containing 1-3 C> (opt. substd.) /
alkenyl <containing 2-3 C> (opt. substd.)
G11 = H / alkyl <containing 1-3 C> (opt. substd.) /
alkenyl <containing 2-3 C> (opt. substd.)
G12 = OH / 46

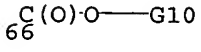


G13 = **N** / **48**

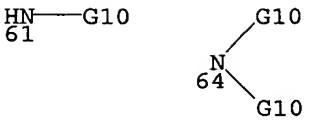


G14 = H / alkyl <containing 1-3 C> (opt. substd.) /
alkenyl <containing 2-3 C> (opt. substd.) / NH2 / 50 / 53 /
OH / 55 / SH / 57 / 59 / CO2H / 66 /
(Specifically claimed: Me)

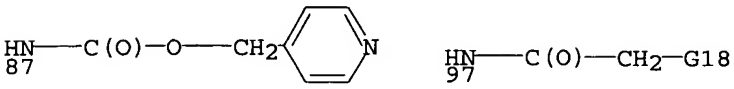


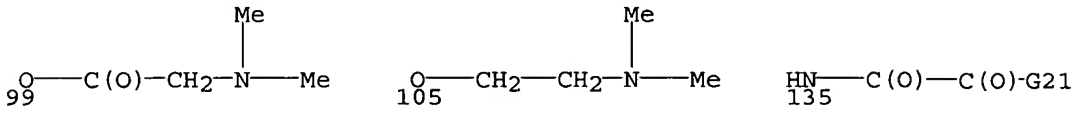


G15 = NH2 / 61 / 64

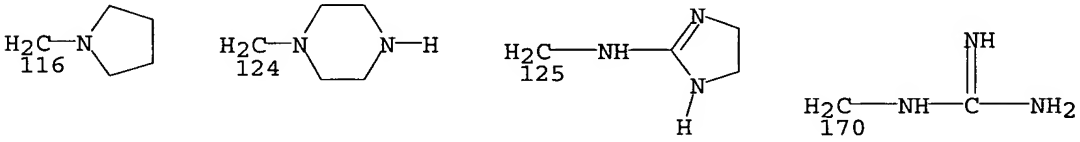


G16 = C(O) / SO2
G17 = Cl / F / Br / Me / OMe / OH / CF3 / OCF3 / OPr-n / NH2 / NMe2 / NHSO2Ph / 87 / 97 / 135 / 99 / 105

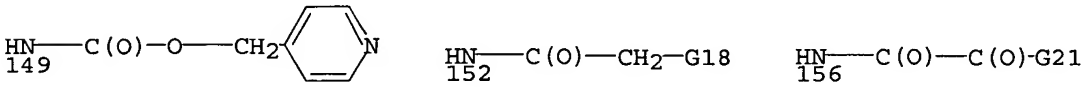


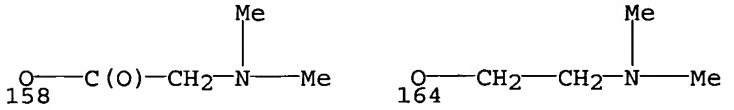


G18 = morpholino / NMe2 / piperazino / pyrrolidino
G20 = Cl / F / Br / Me / Et / Pr-i / OMe / OH / NH2 / CF3 / OCF3 / SMe / OMe / CO2H / CO2Me / CH2NH2 / NMe2 / 116 / CH2OH / (Specifically claimed: 124 / NHC(NH)NH2 / 170 / 125)



G21 = morpholino / piperazino / pyrrolidino
G22 = H / Cl / F / Br / Me / OMe / OH / CF3 / OCF3 / OPr-n / NH2 / NMe2 / NHSO2Ph / 149 / 152 / 156 / 158 / 164





Derivative: or pharmaceutically acceptable salts
Patent location: claim 1
Note: additional ring formation also claimed

L52 ANSWER 14 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 129:54361 MARPAT
TITLE: Preparation of benzisothiazolones and analogs as α1C-adrenergic receptor antagonists

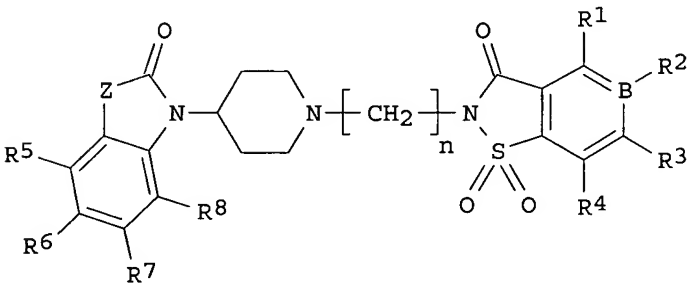
INVENTOR(S): Huff, Joel R.; Lee, Hee-yoon; Nerenberg, Jennie B.; Thompson, Wayne J.; Bell, Ian M.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 57 pp., Cont.-in-part of U. S. Ser. No. 229,276, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5760054	A	19980602	US 1996-722001	19961001
WO 9528397	A1	19951026	WO 1995-US4590	19950413

W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1994-229276 19940413
WO 1995-US4590 19950413

GI



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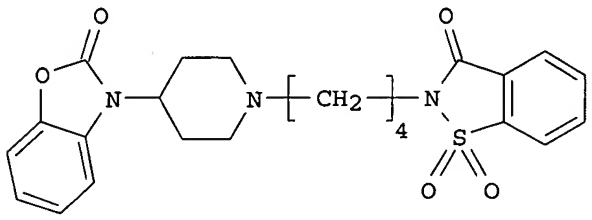


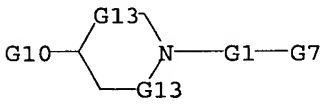
II

AB The invention relates to the claimed title compds. I [n = 3-5; B = C or N; R1, R2, R3, R4 = H, halo, NO2, NH2, (un)substituted alkyl, alkoxy, aryl, heteroaryl, etc.; R5, R6, R7, R8 = H, alkyl, alkenyl, alkoxy; Z = O, S, CH2, NH, NMe] and analogs. Also disclosed are the synthesis and use of the compds. as selective α1C-adrenergic receptor antagonists. The primary application of the compds. is in the treatment of benign prostatic

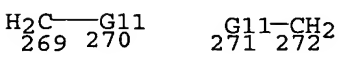
hypertrophy (BPH). The compds. selectively relax smooth muscle tissue enriched in the α1C receptor subtype without inducing orthostatic hypotension. The compds. provide acute relief of BPH by permitting less hindered urine flow. I and analogs are also useful in combination with human 5α-reductase inhibitors, providing both acute and chronic relief from the effects of BPH. Approx. 130 specific invention compds. are disclosed. The cloning and use of a cDNA for a human α1C adrenoceptor in an in vitro assay is described. For instance, alkylation of 1-(4-piperidinyl)-3-benzoxazolin-2-one.HCl (prepared in 4 steps) with 2-(4-bromobutyl)-1,1-dioxido-1,2-benzisothiazol-3(2H)-one in the presence of (i-Pr)2NEt in DMF gave 40% title compound II. Selected compds. showed nanomolar or subnanomolar affinity for human α1C receptor subtype while showing 30-fold lower affinity for human α1A and α1B subtypes (no data).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

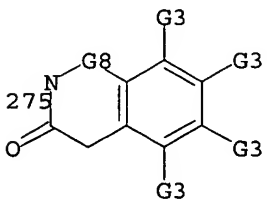
MSTR 2C

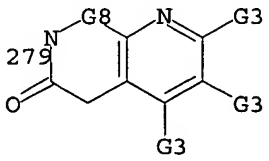


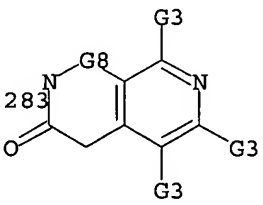
G1 = (3-5) CH2
G3 = H / halo / **NO2** / NH2 / alkyl <containing 1-8 C> (opt. substd. by 1 or more G4) / alkoxy <containing 1-8 C> (opt. substd.) / alkylsulfonyl <containing 1-8 C> / aryl (opt. substd.) / heteroaryl (opt. substd.)
G4 = halo / CF3 / alkyl / alkoxy / aryl / heteroaryl
G5 = H / alkyl <containing 1-8 C> / alkenyl <containing 2-8 C> / alkoxy <containing 1-8 C>
G6 = O / S / CH2 / NH / NMe / 269-21 270-23 / 271-21 272-23 / carbon chain <containing 1-8 C, 0 or more double bonds, no triple bonds>

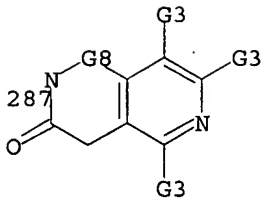


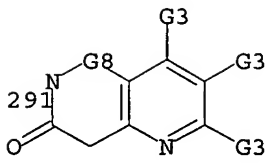
G7 = 275 / 279 / 283 / 287 / 291 / 295 / 299 / 303 / **307** / 311 / 315 / 319 / 323 / 327 / 331 / 335

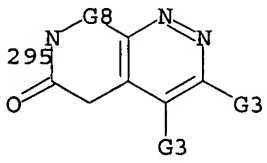


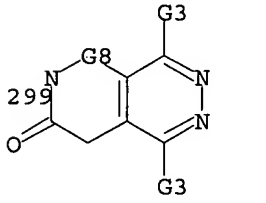


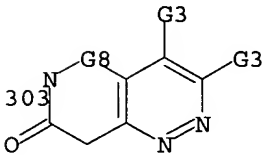


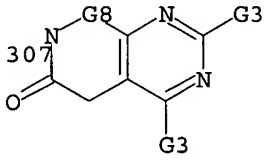


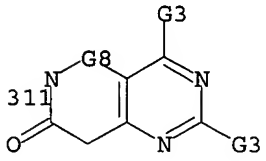


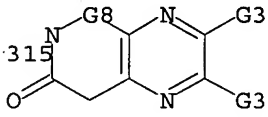


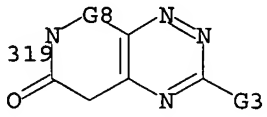


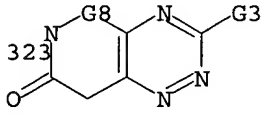


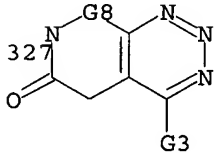


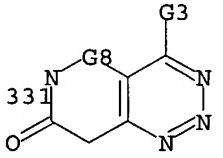


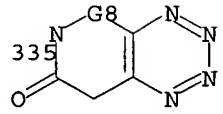




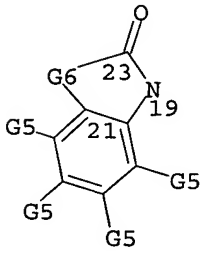


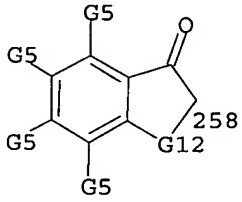






G8 = **C(O)** / SO2
G10 = 19 / 258





G11 = O / S
G12 = NH / CH2 / carbon chain <containing 1-3 C, 0 or more double bonds, no triple bonds>
G13 = **G14** / NH / S / O
G14 = **(0-3) CH2**
Derivative: and pharmaceutically acceptable salts, prodrugs, polymorphs, or metabolites

Patent location: disclosure

Search history

Jaisle 10/824980 07/19/2006

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=> d his full

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                  D SCA
                  D L1

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     FILE 'REGISTRY' ENTERED AT 13:42:21 ON 19 JUL 2006
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L5              7 SEA SSS FUL L3
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                  -2/BI OR 777899-61-3/BI OR 777899-62-4/BI OR 777899-63-5/BI)
L11             5 SEA ABB=ON  PLU=ON  L10 AND L5
L12            11 SEA ABB=ON  PLU=ON  L10 NOT L11
                  D SCA
L13               ANALYZE PLU=ON  L5 1- LC :       3 TERMS
                  D

     FILE 'STNGUIDE' ENTERED AT 13:50:47 ON 19 JUL 2006

     FILE 'MARPAT' ENTERED AT 13:52:35 ON 19 JUL 2006
L14             4 SEA SSS SAM L3
L15            54 SEA SSS FUL L3

     FILE 'STNGUIDE' ENTERED AT 13:53:09 ON 19 JUL 2006

     FILE 'MARPAT' ENTERED AT 13:53:13 ON 19 JUL 2006
                  SAVE TEMP L15 JAI980MARB/A

     FILE 'STNGUIDE' ENTERED AT 13:54:27 ON 19 JUL 2006
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     FILE 'MARPAT' ENTERED AT 13:56:11 ON 19 JUL 2006
L16             STRUCTURE UPLOADED
L17           3 SEA SUB=L15 SSS SAM L16
L18          39 SEA SUB=L15 SSS FUL L16
               SAVE TEMP L18 JAI980MARPC/A

     FILE 'STNGUIDE' ENTERED AT 14:04:18 ON 19 JUL 2006

     FILE 'REGISTRY' ENTERED AT 14:12:28 ON 19 JUL 2006

     FILE 'MARPAT' ENTERED AT 14:12:50 ON 19 JUL 2006
L19             STRUCTURE UPLOADED
L20           2 SEA SUB=L15 SSS SAM L19
L21          13 SEA SUB=L15 SSS FUL L19
               D SCA

     FILE 'STNGUIDE' ENTERED AT 14:17:17 ON 19 JUL 2006

     FILE 'MARPAT' ENTERED AT 14:17:45 ON 19 JUL 2006
               SAVE TEMP L21 JAI980MARPD/A
L22             STRUCTURE UPLOADED
L23           1 SEA SUB=L15 SSS SAM L22
               D SCA
L24           2 SEA SUB=L15 SSS FUL L22
               D SCA
               SAVE TEMP L24 JAI980MARPE/A
               D COST

     FILE 'WPIX' ENTERED AT 14:23:43 ON 19 JUL 2006
L25           2 SEA SSS SAM L3
               D SCA
L26           5 SEA SSS FUL L3
L27           1 SEA ABB=ON  PLU=ON  L26/DCR
               SEL SDCN L26
               EDIT E17-E21 /SDCN /DCN
L28           1 SEA ABB=ON  PLU=ON  (RAFUWH/DCN OR RAFUWI/DCN OR RAFUWJ/DCN OR
               RAFUWK/DCN OR RAFUWL/DCN)
               SEL DCSE L26
L29           1 SEA ABB=ON  PLU=ON  (979788-1-0-0/DCRE OR 979789-0-0-0/DCRE OR
               979790-0-0-0/DCRE OR 979791-0-0-0/DCRE OR 979792-0-0-0/DCRE)
L30           1 SEA ABB=ON  PLU=ON  L28 OR L29
               D SCA

     FILE 'STNGUIDE' ENTERED AT 14:27:01 ON 19 JUL 2006

     FILE 'HCAPLUS' ENTERED AT 14:27:50 ON 19 JUL 2006
L31          12 SEA ABB=ON  PLU=ON  DEWDNEY N?/AU
L32        1091 SEA ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L33           3 SEA ABB=ON  PLU=ON  L31 AND L32
L34           1 SEA ABB=ON  PLU=ON  (L31 OR L32) AND L6
L35          23 SEA ABB=ON  PLU=ON  (L31 OR L32) AND (P38/OBI OR P 38/OBI)

     FILE 'MARPAT' ENTERED AT 14:30:46 ON 19 JUL 2006
L36           0 SEA ABB=ON  PLU=ON  DEWDNEY N?/AU
L37           4 SEA ABB=ON  PLU=ON  L31
L38          20 SEA ABB=ON  PLU=ON  L32
L39           1 SEA ABB=ON  PLU=ON  (L37 OR L38) AND (L21 OR L24)

     FILE 'WPIX' ENTERED AT 14:32:44 ON 19 JUL 2006
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L40           4 SEA ABB=ON  PLU=ON  DEWDNEY N?/AU
L41          97 SEA ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L42           3 SEA ABB=ON  PLU=ON  L40 AND L41
L43           1 SEA ABB=ON  PLU=ON  (L40 OR L41) AND L30

     FILE 'STNGUIDE' ENTERED AT 14:33:31 ON 19 JUL 2006
               D COST

     INDEX 'ABI-INFORM, ADISCTI, AEROSPACE, AGRICOLA, ALUMINIUM, ANABSTR,
     ANTE, APOLLIT, AQUALINE, AQUASCI, AQUIRE, BABS, BIBLIODATA, BIOENG,
     BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAOLD, CAPLUS, CASREACT,
     CBNB, CEABA-VTB, CERAB, CHEMINFORMRX, CHEMSAFE, ...' ENTERED AT 14:35:22
     ON 19 JUL 2006
               SEA (DEWDNEY N?/AU) AND (GOLDSTEIN D?/AU)
              ---------
              3   FILE CAPLUS
              0*  FILE CBNB
              0*  FILE CIN
              3   FILE DPCI
              3   FILE EPFULL
              0*  FILE IFICLS
              3   FILE IFIPAT
              0*  FILE IMSDRUGNEWS
             12   FILE INPADOC
              0*  FILE NLDB
              0*  FILE NUTRACEUT
              0*  FILE PATDPA
              0*  FILE PATDPASPC
              3   FILE PCTFULL
              0*  FILE PCTGEN
              0*  FILE PHARMAML
              0*  FILE PHIC
              0*  FILE PHIN
              0*  FILE RDISCLOSURE
              3   FILE USPATFULL
              3   FILE WPIDS
              3   FILE WPINDEX
L44            QUE ABB=ON  PLU=ON  (DEWDNEY N?/AU) AND (GOLDSTEIN D?/AU)
              ---------

     FILE 'HCAPLUS' ENTERED AT 14:37:29 ON 19 JUL 2006
               D SCA TI L35

     FILE 'STNGUIDE' ENTERED AT 14:38:30 ON 19 JUL 2006

     FILE 'REGISTRY' ENTERED AT 14:38:41 ON 19 JUL 2006

     FILE 'HCAPLUS' ENTERED AT 14:38:45 ON 19 JUL 2006
               D STAT QUE L33
               D STAT QUE L34
               D STAT QUE L35
L45           23 SEA ABB=ON  PLU=ON  (L33 OR L34 OR L35)

     FILE 'MARPAT' ENTERED AT 14:39:29 ON 19 JUL 2006
               D STAT QUE L39

     FILE 'WPIX' ENTERED AT 14:40:18 ON 19 JUL 2006
               D STAT QUE L42
               D STAT QUE L43
L46            3 SEA ABB=ON  PLU=ON  (L42 OR L43)
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     FILE 'STNGUIDE' ENTERED AT 14:40:45 ON 19 JUL 2006

     FILE 'HCAPLUS, WPIX, MARPAT' ENTERED AT 14:41:05 ON 19 JUL 2006
L47          24 DUP REM L45 L46 L39 (3 DUPLICATES REMOVED)
                    ANSWERS '1-23' FROM FILE HCAPLUS
                    ANSWER '24' FROM FILE WPIX
               D IBIB ABS HITIND HITSTR L47 1-23
               D IBIB ABS HITSTR L47 24

     FILE 'STNGUIDE' ENTERED AT 14:42:26 ON 19 JUL 2006

     FILE 'REGISTRY' ENTERED AT 14:42:43 ON 19 JUL 2006
               D STAT QUE L6
L48            7 SEA ABB=ON  PLU=ON  L6 NOT L45
               D COST

     FILE 'HCAPLUS' ENTERED AT 14:44:59 ON 19 JUL 2006
               D STAT QUE L6
L49            1 SEA ABB=ON  PLU=ON  L6 NOT L45

     FILE 'WPIX' ENTERED AT 14:45:43 ON 19 JUL 2006
               D STAT QUE L30
L50            0 SEA ABB=ON  PLU=ON  L30 NOT L46

     FILE 'MARPAT' ENTERED AT 14:46:10 ON 19 JUL 2006
               D STAT QUE L21
               D STAT QUE L24
L51           13 SEA ABB=ON  PLU=ON  (L21 OR L24) NOT L39

     FILE 'BEILSTEIN' ENTERED AT 14:47:23 ON 19 JUL 2006
               D STAT QUE L8

     FILE 'HCAPLUS, MARPAT' ENTERED AT 14:47:53 ON 19 JUL 2006
L52           14 DUP REM L49 L50 L51 L8 (0 DUPLICATES REMOVED)
                    ANSWER '1' FROM FILE HCAPLUS
                    ANSWERS '2-14' FROM FILE MARPAT
               D IBIB ABS HITIND HITSTR L52 1
               D IBIB ABS HIT L52 2-14

     FILE 'STNGUIDE' ENTERED AT 14:50:31 ON 19 JUL 2006


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   18 JUL 2006  HIGHEST RN 894196-03-3
     DICTIONARY FILE UPDATES:  18 JUL 2006  HIGHEST RN 894196-03-3

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     REGISTRY includes numerically searchable data for experimental and
```

predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 17, 2006 (20060717/UP).

FILE HCAPLUS

FILE COVERS 1907 - 19 Jul 2006 VOL 145 ISS 4
FILE LAST UPDATED: 18 Jul 2006 (20060718/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BEILSTEIN
FILE LAST UPDATED ON JUNE 16, 2006

FILE COVERS 1771 TO 2006.
FILE CONTAINS 9,606,495 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

****
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *
****

NEW
*** PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.**

*** NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.**

FILE MARPAT
FILE CONTENT: 1961-PRESENT VOL 145 ISS 1 (20060714/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US	2006118302	08 JUN 2006
DE	102004053653	04 MAY 2006
EP	1653548	03 MAY 2006
JP	2006112980	27 APR 2006
WO	2006053912	26 MAY 2006
GB	2419594	03 MAY 2006
FR	2877004	28 APR 2006
RU	2275374	27 APR 2006
CA	2518664	10 MAR 2006

Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

FILE WPIX
FILE LAST UPDATED: 14 JUL 2006 <20060714/UP>
MOST RECENT DERWENT UPDATE: 200645 <200645/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

FILE STNINDEX

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